IMPLICATIONS OF FEED ADDITIVES IN THE MITIGATION OF HEAT STRESS IN CATTLE

by

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As members of the Master's Committee, we certify that we have read the thesis prepared by Matthew Vander Poel, titled Implications of Feed Additives in the Mitigation of Heat Stressed Cattle and recommend that it be accepted as fulfilling the dissertation requirement for the Master's Degree.

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Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to the Graduate College.

I hereby certify that I have read this thesis prepared under my direction and recommend that it be accepted as fulfilling the Master's requirement.

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ABSTRACT

Nutritional supplements have been used to mitigate heat stress in cattle. A series of experiments were conducted under controlled environment conditions in the Animal Research Complex (ARC) to evaluate the value of nutritional intervention on mitigation of heat stress **(HS)** in cattle. Previous research and literature have shown mixed results in terms of performance benefits.

In the first study, we evaluated the use of a proprietary yeast cell extract to help mitigate the effects of hyperthermia on growth development by improving metabolic and immune functions. Twelve crossbred Hereford steers (250 ± 100 kg) were randomly assigned to one of two dietary groups: control group **(CON)** received 56.7 g of placebo/hd/day; the feed additive group **(BA)** received 56.7 g of BA/hd/day. Steers were randomly assigned to one of two tie stall rooms with 6 steers per room and 3 steers per treatment/room. Rooms were exposed to cyclical daily temperature humidity index **(THI)** of 70 - 81 and 27 – 39 for HS and the thermoneutral **(TN)** rooms respectively for a total of 15 days. Average daily water consumption and average daily gain were calculated at the end of the experimental period. Heat stress increased water consumption ($P<0.001$), respiration rate ($P<0.001$), and skin temperature ($P<0.001$) and tended to increase rectal temperature ($P<0.06$). Supplementation with BA tended to reduce rectal temperatures ($P<0.06$) in heat stressed cattle. Exposure to heat stress lowered serum glucose ($P<0.01$) and insulin ($P<0.01$) while increasing NEFAS ($P<0.01$) and TAG ($P<0.01$). Supplementation with BA lowered TAG ($P<0.05$) and glucose ($P<0.05$). HS and BA supplementation had no effect on serum cortisol levels. Results of this study suggest that HS exposure for 15 days had performance and metabolic impacts in crossbred Hereford steers.

Supplementation with the dietary BA alleviated some of the daily metabolic effects associated with heat exposure.

The objective of the second study was to evaluate the effect of feeding a dietary supplement (PMI Nutritional Additives, Arden Hills, MN) on the HS response in multi-parturient dairy cows in mid lactation. Two pens of cows at a commercial dairy were fed either control (CON) or additive **(YB)** at 113 g/cow per d for two weeks prior to arrival. Study cows (n=12) were balanced in days in milk **(DIM)**, milk production, and parity (111.91±4.85 d, 33.67±0.96 kg/d, and 2.25±0.18). Cows were randomly selected from both groups (6 TRT and 6 CON) and housed in environmentally controlled chambers for 18 d and fed appropriate diet. Cows were subjected to 7 d of TN conditions, 7 d of HS, and 4 d of recovery **(REC)** under TN conditions. HS increased RT (P<0.0001), RR (P<0.0001), BUN (P<0.0001), insulin (P=0.04), neutrophil (P=0.009), and water intake (P=0.0005). HS decreased lymphocyte (P=0.0008), DMI (P=0.0007), energy corrected milk (ECM, P=0.01), and 4% fat corrected milk (FCM, P=0.02). YB decreased the feed efficiency ratio (P=0.03). YB had no effect on blood parameters. There was a treatment x environment interaction with cows fed YB having lower feed efficiency (P=0.02) during peak thermal loads than CON. Results of this study suggest that HS exposure had performance and metabolic impacts in mid lactation cows. Supplementation with YB alleviated some of the performance effects associated with HS.

The research results support that feed additives have the potential to mitigate the negative effects of heat stress but doesn't undermine the importance of other nutritional and management strategies that are in use.

Chapter 1

Literature Review

INTRODUCTION

In today's dairy industry, one of the prominent concerns is the response of cattle to heat stress. Cattle experience heat stress when any combination of environmental factors such as temperature, humidity, solar radiation, air movement, and precipitation cause the ambient temperature to exceed body temperature (Armstrong, 1994). Summer in the Northern Hemisphere has a natural tendency to be warmer than the other seasons and there are observations that indicate an increase in variability of those temperatures (Schär et al., 2004). Climate change places significant costs on areas that are susceptible to drastic changes in environments (Adams et al., 1998). At the beginning of the century, it was estimated the lost national annual revenue in economic loss between $1.9 and $2.7 billion per year and about $900 million to just the dairy industry alone due to heat stress (St-Pierre et al., 2003). This is problematic for animal producers since a majority of large-scale cattle operations are in regions that experience seasonal stressors that influence productivity (Collier et al., 2006a).

In order to maintain optimum production, cattle must be inside a range of temperature that is referred to as the thermal neutral zone. The thermal neutral zone is dependent on the production level as well as the physiological status of the animal (Hahn, 1999). The thermal neutral zone is an area that is between the lower and upper critical temperatures. The lower critical temperature is above the environmental temperature that the body produces extra heat to meet thermostatic requirements. The lower critical temperature is estimated between -4 and 2˚C depending on production performance in cattle (Hamada, 1971). The upper critical temperature

is defined as the environmental temperature at which the body begins to store heat and thus loses production. It was reported to be between 25 and 26˚C (Berman et al., 1985). The thermal neutral zone for lactating cattle is estimated to be -1.7 to 21˚C (Johnson and Vanjonack, 1976).

Heat stress occurs when the upper critical temperature is exceeded. The balance between the amount of energy the animal can exchange with the environment and the amount of energy produced through metabolic processes is exceeded resulting in heat storage in the animal and increased core body temperature. Cattle mount a response to heat stress that changes the behavior, metabolism, and physiology (Collier and Gebremedhin, 2015). Heat stress results in an increase in maintenance costs and initiation of physiological acclimation responses (Rhoads et al., 2009). This results in a loss of production (growth, lactation, etc.) and thus a decrease in profitability.

Environmental (shade, fans, evaporative cooling), genetic, and nutritional strategies have been utilized to meet the needs of cattle and to negate the effects of heat stress. One nutritional strategy is to feed products that alter the rumen microbial population that are impactful (Edwards et al., 2008). Yeasts and other probiotics have the potential to have positive effects on the utilization of nutrients in ruminants (Oeztuerk and Sagmanligil, 2009; Peng et al., 2012).

Heat Stress

Indicators

Temperature-Humidity Index

The temperature-humidity index (THI) is a combination of measured effects of ambient temperature and relative humidity to indicate the thermal stress level that cattle are experiencing (Berman, 2005; Bohmanova et al., 2007; West, 2003). It was first developed by Thom (1958)

and used for dairy cows by Berry et al. (1964). Extensive research has been done in regards to calculating THI due to the increase in production of cows. There has been little work done for beef cattle (Diaz et al., 2018). For beef cattle, the heat load index is used instead of THI and additionally takes into consideration solar radiation, wind, and stage of production (Gaughan et al., 2008). Multiple THI calculations have been proposed due to various production variables (Bohmanova et al., 2007). In regards to lactating dairy cows, the current agreement is based on work done by Zimbelman et al. (2009), where THI above 68 is considered to be stressful (Fig. 1.1). Stress levels are divided into 4 groups: 1) stress threshold (THI 68-71), 2) mild – moderate (72-79), 3) moderate – severe (80-89), and 4) severe (90-98).

Body Temperature

The range for body temperatures for cattle is reported as 38.6 ± 0.5˚C (Anderson, 1993). An increase of 1˚C is sufficient enough to reduce performance of cattle (Kadzere et al., 2002). There is variation between species as reported by (Srikandakumar and Johnson, 2004) when cattle were exposed to an increase in THI from 72 to 93.

Rectal temperature is used to represent the thermal balance and used to indicate the effects of heat stress on growth parameters in cattle (Hahn, 1999; West, 1999). Finch has demonstrated there is a difference between breeds with *Bos indicus* having a lower mean rectal temperature than *Bos taurus* (Finch, 1986). Vaginal temperatures are another means of measuring core body temperature. Research using an intravaginal device such as a continuous intravaginal drug release (CIDR) can record temperature as cattle throughout the day (VanBaale et al., 2006).

Respiration Rate

Respiration rate is a rough indicator of the heat load due to the changes in physiology of the animal as it undergoes heat stress to maintain equilibrium (Kadzere et al., 2002). At thermal neutral temperatures, the respiration rate for cattle is considered to be 20 breaths per minute (Thomas and Pearson, 1986). As ambient temperatures become elevated and cattle experience heat stress, breaths per minute can exceed 100 at 32˚C (Johnston et al., 1959). It has been reported there is a difference between respiration rate with cattle breeds (Kadzere et al., 2002). Later in this review, the importance of respiration rate will be discussed with regards to insensible (latent) heat loss. This becomes an issue as relative humidity increases and the ability for evaporative cooling decreases because latent heat loss works on a vapor pressure gradient rather than a temperature gradient.

Behavior

Besides altering the physiology and metabolism of cattle, heat stress also alters the behavior to minimize heat gain and maximize heat loss. High producing cows have the highest heat load of the cattle and thus are the most susceptible to heat stress. Some noticeable behavioral changes are increased water intake (low producing cattle), seeking shade, reduced feed intake, altered estrous behavior, standing, and respiration rate (Jones and Stallings, 1999).

Water loss occurs through 4 primary routes: cutaneous and pulmonary evaporation, feces, and urine. Cattle experience dehydration at 12% body weight water loss (Roussel, 1999). Water intake increases with the rise in ambient temperature to a rate of 1.2 kg/ ˚C (West, 2003). However, it has been noted that there is a decrease in water intake in cows producing over 25 kg of milk due to the decrease in milk production as well as metabolic rate (Collier et al., 2018).

Cattle use shade when given the opportunity and the use of shade has been shown to alleviate some of the negative responses seen in an increased heat load (Finch, 1984; Roman-Ponce et al., 1977; Valtorta et al., 1997). When feedlot cattle were given the choice between misting and shade, they preferred shade and had increased performance (Marcillac-Embertson et al., 2009; Mitlohner et al., 2002). Although dairy cows preferred shade as ambient temperature increased, sprinklers were more efficient in decreasing the heat load (Schütz et al., 2011; Schütz et al., 2010). Actively seeking shade is preferred over drinking or eating by animals (Jones and Stallings, 1999).

The decrease in feed intake from heat exposure is a primary response observed in cattle at different stages: bull calves (Yazdi et al., 2016) and lactating dairy cows (Rhoads et al., 2009). This reduction in voluntary feed intake has been widely accepted as a major influence on production. According to the National Research Council (NRC, (2007), when ambient temperatures exceed 25˚C, cattle will demonstrate decreased intake. Renquist (2019) proposes that hypophagia is the result of depressed visceral blood flow from excess sympathetic tone. It has been shown that ruminants shift blood from the viscera to the periphery (Hales, 1973). Another factor that has been considered is the decrease in gut motility (Attebery and Johnson, 1969).

Cattle will exhibit extensive standing behavior when ambient temperatures increase. Albright and Arave (1997) noted a decrease in resting behavior when cattle were heat stressed. When THI exceeded 68 units, there was a decrease in resting (Cook et al., 2007). This change in behavior leaves cattle more susceptible to hoof diseases and laminitis (Cook et al., 2007).

Thermoregulatory Mechanisms

Cattle are homeotherms that maintain a body temperature above the ambient temperature. Metabolic heat and dissipation of heat from the cattle to the environment dictates the core body temperature (Hansen, 2004). Cattle are able to dissipate heat through a thermal gradient: conduction, convection, and radiation. The term for this heat loss strategy is sensible heat loss. Conduction is defined as the heat flow between two reservoirs in direct physical contact. It is important to note that heat flows from hot to cold. In conduction, energy is transferred through molecular collisions in which there are types of materials: gas, liquid, and solids. Due to air having low thermal conductivity, the net heat gain is relatively small in comparison to other types of material (Yousef, 1985). Bedding is an important factor for conduction and cattle with a high metabolic heat load had the greatest preference for the lowest temperature material (Cummins, 1998).

Convection is the heat exchange with air that surrounds the surface of a body. During low ambient temperatures, the heat from the animal's surface is exchanged with the air, cooling the body. The body temperature increases; however, when the air temperature is greater than the skin temperature and heat movement to the animal will be supported till air temperature equals skin temperature (Kadzere et al., 2002). In cattle, vasodilation is increased in hot environments but isn't a major heat dissipation mechanism due to the body mass (Berman et al., 1985).

Radiation is generated from the emission of electromagnetic waves. It is noted that shorter wavelengths are generated from hotter bodies (e.g. the sun). Animals receive short wave radiation from solar energy and are able to radiate long waves to the environment (Yousef, 1985). There is a difference in heat gain by radiation with objects that have different color and texture (Cena and Monteith, 1975).

When environmental temperatures exceed body temperature, cattle are unable to dissipate metabolic heat by means of sensible heat loss. They resort to another heat strategy known as latent heat exchange. Latent heat exchange is an autonomic response by the cattle under heat stress. The mechanisms are sweating and panting which require a vapor pressure gradient. Evaporative cooling is crucial and develops a heat gradient when ambient temperatures are higher than body temperatures (Maia and Loureiro, 2005). Air velocity is an important factor influencing heat transfer (Kadzere et al., 2002).

Sweating is one of the most important thermoregulation mechanisms exhibited by cattle in high temperatures but not high humidity environments. As humidity increases, the effectiveness of the evaporation of sweat decreases (Maia and Loureiro, 2005). There are two types of sweating observed in cattle: insensible and thermal. Insensible sweating is perspiration that exits all the time unless there is no vapor pressure gradient, 100% humidity. Thermal sweating is the cooling mechanism as cattle experience elevated temperatures. The apocrine gland of the hair follicle has one sweat gland associated with it. Thus, the greater the hair density, the greater the number of sweat glands. The peak sweating rate of cattle has been calculated to be around 200 to 300 $g/m^2/h$ (Berman, 2005). There is a difference in sweating between *B. indicus* and *B. taurus* due to hair density and length (Gebremedhin and Wu, 2001).

Another route of insensible heat loss in cattle is by panting. Two ways that respiration can exchange heat is through evaporation of water in the lungs and also increasing the temperature of air that is inhaled (Brouk et al., 2001). Johnson and Vanjonack (1976) demonstrated that at the same ambient temperature increasing the relative humidity 25% resulted in a decrease in milk production. The increase in humidity reduced evaporation which caused a rise in body temperature.

A consequence of excessive panting is respiratory alkalosis caused by an increase in blood pH. Blood pH is a high homeostatic priority and depends on the carbonic acid and bicarbonate base (Coppock et al., 1982). Water and carbon dioxide form carbonic acid with there being an intermittent form that is a hydrogen ion and bicarbonate. The blood pH shift results from excessive carbon dioxide being expired which favors the shift of carbonic acid to water and carbon dioxide (Dale and Brody, 1954). Panting increases carbon dioxide loss by pulmonary respiration, thus reducing carbonic acid concentration in the blood and raising the pH which causes respiratory alkalosis (Benjamin, 1981). Schneider et al. (1988) described renal compensation to this shift in pH by having an increase in urine pH. Elevated urine pH is caused by an increase in bicarbonate and sodium being filtered out by the kidneys (Bianca, 1965). The decrease in the blood concentration of bicarbonate leaves less bicarbonate available for rumen buffering and lowers the ruminal pH of cows (Bandaranayaka and Holmes, 1976). These compensatory mechanisms favor metabolic acidosis during cooler temperatures when panting isn't as demanding (West, 2003).

Effects on Performance

Heat stress increases the maintenance energy requirements in cattle (Beede and Collier, 1986; Fuquay, 1981; McDowell et al., 1969; Morrison, 1983). Fox and Tylutki (1998) estimated that the maintenance cost to increase as much as 30% in heat stressed lactating cattle. Metabolic rate potentially increases during the acute phase but not the chronic phase of heat stress (Bianca, 1965) that is linked to the body mounting a response to the stress. Others have speculated that animals have a decrease in maintenance cost and body expenditure for mild stress but increase

during the chronic phase (Kleiber, 1961; Yunianto et al., 1997). This shift from production to maintenance has implications on the performance due to altered metabolisms.

A decrease in dry matter intake (DMI) and milk yield are negatively correlated (Johnson and Ragsdale, 1962). As temperature increases, milk production declines. Bohmanova et al. (2007) showed different milk production rates per unit of THI. A decrease of 35-40% in milk production is not uncommon when cows are exposed to heat stress (West, 2003). Collier et al. (1981) reported that the maximum response of heat stress on milk yield is seen 24-48 hours after exposure due to change in the metabolic state of the cows. Although a decrease in feed intake predicts a decline in milk yield, feed intake only accounts for 35-50% of the reduction of milk production with heat stressed cows (Rhoads et al., 2009; Wheelock et al., 2010).

The stage of lactation and parity of the cow also plays a role in milk yield during heat stress (Maust et al., 1972). Stage of lactation is broken up into different categories by days in milk (DIM): early (<100 DIM), mid (100-180 DIM), and late (>180 DIM). Early lactation cows show the least effects of heat stress due to the utilization of body reserves to offset the initial negative energy balance brought by lactation demand (Maust et al., 1972). This doesn't exempt early lactation cows from negative complications from heat stress. Multiparous cows are more vulnerable to heat stress because of increased milk production, body weight, feed intake, and metabolic activity in comparison to primiparous cows (West, 1994).

Since heat stress lowers feed intake, there is a direct impact on growth performance. Beef cattle begin to suppress dry matter intake after the ambient temperature has exceeded 30 ˚C with relative humidity below 80% (Bernabucci et al., 2010). Beef cattle production losses aren't as large as dairy cattle and much of that is credited to the metabolic heat load. Baumgard and Rhoads (2013) state that three possibilities for this difference are the increased surface area to

mass ratio, lower rumen heat production, and lower metabolic heat production by body weight. Heat stress can have some positive effects on growth performance in cattle. Research by O'Brien et al. (2010) showed that heat stress impairs average daily gain and feed efficiency for growth which can cause compensatory growth. Compensatory gain/growth is seen in growing cattle after there is a feed restriction (Yambayamba et al., 1996). Hahn et al. (1974) showed that cattle exposed to various temperatures (20, 30.9, and 37.7 ˚C) experienced compensatory gain with the 30.9 ˚C after 2 weeks of heat stress was relieved; however, this effect doesn't occur after severe heat stress.

One aspect of growth performance is with skeletal muscle. Heat stress can cause a shift towards greater muscle marbling and fat deposition instead of subcutaneous depot (Gregory, 2010). Having heat stress relief has been shown to decrease dark cutters (Mitlöhner et al., 2001). Kadim et al. (2004) reported higher pH values, less shear force, and darker meat in the *M. longissimus thoracis* in beef cattle exposed to a hot season compared to the cool season.

Kadzere et al. (2002) reported an increase in health problems in cattle during warm summer months. An increase of retained placentas and metritis cases in cows that partitioned in summer was 12% higher than the rest of the year (DuBois and Williams, 1980). Pavlicek et al. (1989) observed an increase of 11% in cases of ketosis in dairy cows in the summer compared to cooler months. The number of mastitis incidences has been reported during the warmer months (Morse et al., 1988; Waage et al., 1998).

Rumen acidosis is a compensatory side effect of respiratory alkalosis (West, 2003). However, there are other ways that can cause rumen acidosis in cattle. It can be caused by feed changes such as low fiber diets and high energy diets, which are often used during times of heat stress to compensate for reduced feed intake. Cows ruminate less and have decreased buffers

(saliva) entering the rumen. Kadzere et al. (2002) stated that the reduction of bicarbonate in the saliva makes the rumen more susceptible to acidosis.

Reproduction efficiency is affected in cattle during heat stress. Heat stress impacts the following: altered follicular dynamics, decreased estrous behavior and duration, decreased quality of the oocyte, lower conception and pregnancy rate, as well as premature embryonic death (De Rensis and Scaramuzzi, 2003; Kadzere et al., 2002; Thatcher and Collier, 1986). Follicular dynamics are altered with heat stress. The lengthening of the follicular wave and the delay of follicle selection cause unfavorable effects on the oocyte (Badinga et al., 1993; Roth et al., 2001). Several studies have shown a decline in follicular steroidogenesis as well as a greater number of follicles with the decline in follicular dominance (Howell et al., 1994; Wolfenson et al., 1995). Oocyte growth is compromised with the altering of hormones (progesterone, luteinizing hormone, and follicle-stimulating hormone) as well as estrous cycle dynamics (Ronchi et al., 2001). Ryan and Boland (1991) reported an increase in twinning in the summer due to the reduction of individual follicular dominance and an increase in multiple dominant follicles that arise.

Estrous behavior is a critical time period for producers to successfully breed. Barr (1975) attributes missed heats with having longer calving intervals as well as a decrease in income. While cows subject to heat stress, there will be an increase in silent ovulations and anestrus events, decreases in duration and intensity of estrus; all which contribute to the decrease in detection of estrus (Gwazdauskas et al., 1981; Pennington et al., 1985; Thatcher and Collier, 1986). These changes are credited to hormonal changes with a reduction in gonadotropin releasing hormone, luteinizing hormone, and estradiol (De Rensis and Scaramuzzi, 2003).

A decrease in conception rate is credited to hormonal changes that alter uterine blood flow which increases uterine temperature (García-Ispierto et al., 2007; Roman-Ponce et al., 1978). The altered uterine blood flow is also correlated to early embryonic death due to variation in nutrient uptake and growth (Biggers et al., 1987).

Collier et al. (1982) showed that cows that experienced heat stress during late gestation had reduced placental function and lower calf birth weights compared to cooled cows.

Nutrient Partitioning

Acclimation & Adaptations

Acclimation is the behavioral or physiological changes occurring within the life span of an organism to modify strain (Bernabucci et al., 2010). This is a homeorhetic process that takes days to several weeks to occur. Acclimation is composed of an acute and a chronic response. If the stress is removed animals return to the non-acclimated state. However, if the stress becomes chronic over several generations these responses become fixed genetically and result in "adaptation". Adaptation varies among cattle species with the *Bos indicus* having more thermotolerant genes (Hansen, 2004). The result of acclimation results in a decrease in productivity in cattle, most notable in higher producing cattle (West, 2003). Igono et al. (1992) showed cattle need sufficient time to lose heat gained from the previous heat load especially at night. High producing cows generate more heat than low producing cows and thus need more time to dissipate the heat load. This leads high producing cows to have a higher heat load which is shown with having elevated milk temperatures compared to low producing cows with p.m. milking (Igono et al., 1985). Because of this high heat load, high producing cows are not able to

achieve their previous milk production prior to heat stress compared to low producing cows (Igono et al., 1985).

The acute phase of heat stress for acclimation involves the heat shock response (Carper et al., 1987). Cells respond to maintain homeostasis (Arya et al., 2007) and upregulate genes associated with stress response and repair and down-regulate cellular metabolism genes (Collier et al., 2006b). Heat shock transcription factor 1 (HSF1) is responsible for the heat shock protein (HSP) activation (Pirkkala et al., 2001). HSP have three activities: chaperone activity, regulation of cellular redox state, and regulation of protein turnover (Macario and de Macario Conway, 2007). Results for the influence of HSP on milk protein have shown that as the number of HSP and increased, casein concentration decreased in mammary epithelial cells (Hu et al., 2016).

Adaptation is the reduction of physiological strain by stress from the environment through genetic changes. Chronic responses result in a more fit phenotype and reflects genetic adaptation (Collier et al., 2006a).

Negative Energy Balance

During heat stress, cattle will decrease their DMI and initiate metabolic and physiological adjustments that shift from production gains to maintenance requirements (Bernabucci et al., 2010). These changes in postabsorptive nutrient partitioning are required to support production such as milk and skeletal muscle synthesis and are described as “glucose sparing” when on an inadequate-plane of nutrition (Bauman and Currie, 1980). The central nervous system, erythrocytes, and immune cells primarily oxidize glucose. To compensate for the shift in metabolism, lactate levels are elevated during heat stress (Kahl et al., 2015). It is speculated that

most of the lactate is coming from muscle and the gastrointestinal tract (Baumgard and Rhoads Jr, 2013).

Metabolic changes to support growth in high-priority tissues such as skeletal muscle during feed restriction are applied (Van Milgen and Noblet, 2003). A combination of decreased insulin concentration and insulin sensitivity favor lipolysis in adipose tissue and non-esterified fatty acid (NEFA) mobilization (Mersmann, 1987). By increasing β-oxidation of fatty acids to generate energy, glucose is conserved.

Negative energy balance (NEBAL) for lactation happens at parturition to mid-lactation because the cow can't consume enough nutrient to meet the costs of maintenance and milk production (Drackley, 1999). Somatotropin increases during negative energy balance and causes shifts in carbohydrate and fatty acid metabolism (Bauman and Currie, 1980). Bauman and Vernon (1993) attribute lipolytic properties to somatotropin with increasing responsiveness to β-adrenergic signals and inhibiting insulin mediated pathways. Increased NEFA and ketones provide a source of energy for lactating cows. Glucose is partitioned to the mammary gland and its role as a fuel source is decreased (Bell, 1995).

Endocrine

Heat stress causes a variety of regulation changes depending on the duration of stress. Homeostatic regulation is an acute response that happens within seconds or minutes to heat stress. Homeorhetic mechanisms alter acclimation for the chronic responses which can take days or weeks. Collier (2006a) states that acclimation is under endocrine regulation during this stress event. Fluctuation in hormone concentrations and target tissue responses are part of the altered metabolism to maintain the physiological state of the acclimatized animal.

Insulin is a peptide hormone produced in the beta cells of the pancreas. It a regulator of carbohydrate and lipid metabolism. Glucose transporter type 4 is stimulated by insulin and is found mostly in skeletal muscle and adipose tissue. Vernon (1992) described insulin as an antilipolytic hormone. Heat stressed cattle have elevated levels of insulin (Wheelock et al., 2010). This causes hypoglycemia in heat stressed cows (Wheelock et al., 2010) and bulls (O'Brien et al., 2010).

Somatotropin (ST) is a prominent lactogenic hormone (Bauman and Vernon, 1993). During heat stress, ST decreases which may be the result of the cattle reducing its metabolic heat load (Igono et al., 1988). There is also a response which corticotropin releasing hormone (CRH) stimulates ST release from the hypothalamus while inhibiting production of ST and other metabolic hormones from the pituitary (Collier et al., 2006a).

Prolactin is another lactogenic hormone that is increased during periods of heat stress (Alamer, 2011; Thatcher, 1974). Baumgard and Rhoads (2013) suggest that prolactin may correspond with insulin. β cell proliferation by prolactin in vitro (Arumugam et al., 2010) and glucose stimulated secretion (Ben-Jonathan et al., 2006) support elevated prolactin levels with insulin levels.

The hypothalamus releases CRH that acts on the anterior pituitary to release the precursor, adrenocorticotropic hormone. This hormone produces glucocorticosteriods, mostly cortisol. The hypothalamic-pituitary-adrenal axis is activated during stress events and increases plasma concentrations (Silanikove, 2000). Heat stressed animals show elevated levels of cortisol in acute response to stress that ultimately alters physiological processes that begin the acclimation process (Christison and Johnson, 1972; Wise et al., 1988). During periods of

prolonged heat exposure, cattle will undergo chronic acclimation which shows a decreased level of cortisol (Christison and Johnson, 1972).

Thyroid hormones are important for the regulation of thermogenesis and are determinants for metabolic rate of tissues (Silva, 2006). Thyroxine (T_4) is synthesized in the thyroid gland and has no inherent biological activity. Triiodothyronine (T_3) is the metabolically active hormone which is produced by the removal of one iodine from T_4. Cattle have declining levels of T_3 and T_4 in response to HS in order to suppress metabolic heat production (Johnson et al., 1988). Kahl et al. (2015) reported that while HS depresses thyroid hormone concentrations, inflammation suppresses T_3 generation and pituitary-thyroid axis in steers.

Tumor necrosis factor-alpha (TNFα) is a pro inflammatory cytokine that is produced by various cell types, especially macrophages and adipocytes. It plays a role in triggering the acute-phase response in which the liver increases production of acute phase proteins (Venteclef et al., 2011). These acute phase proteins play a role in systemic reaction to inflammation which is characterized by opsonization, regulation of inflammation, and scavenging of toxic substances (Ceciliani et al., 2012). TNFα administration in mid lactation cows has been shown to decrease milk yield by 15% (Kushibiki et al., 2003). Yuan et al. (2013) reported that cows that had induced inflammation from TNFα had an increase in health incidences: ketosis, mastitis, respiratory diseases, metritis, and milk fever.

Carbohydrate

Glucose is a primary nutrient for growth in cattle as well as milk synthesis in lactating cows. Very little glucose is absorbed in the intestines and originates from hepatic and renal gluconeogenesis (Aschenbach et al., 2010). Short chain fatty acids (propionate, isobutyrate, and

valerate), lactate, alanine, glycerol, and other amino acid are glucose precursors with propionate (60-74%) being the most important (Aschenbach et al., 2010; Drackley et al., 2001). Glucose is readily oxidized in tissues. It is also the substrate for lactose synthesis which is the primary osmotic driver in milk production. Glucose is partitioned to the mammary gland during early lactation and inadequate feed intake (Bell, 1995).

During HS, cattle are more dependent on glucose for being the main energy substrate instead of fatty acids (Baumgard and Rhoads, 2012). Wheelock et al. (2010) were able to show lactating cattle that utilize glucose as a fuel source with the down-regulation of milk synthesis. Heat stressed cows secreted 200-400 g/d less milk lactose than the thermal neutral pair-fed control cow (Wheelock et al., 2010).

Lipid

Volatile fatty acids (VFA) are fatty acids that have six or less carbons. They are produced as byproducts of microbial fermentation of carbohydrates and generate approximately 70% of the energy needs for ruminants (Bergman, 1990). The predominant VFAs produced in the rumen, colon, and cecum are the following: acetate (2C), propionate (3C), and butyrate (4C) (Richardson et al., 1976).

Acetate is primarily used for energy production when converted to Acetyl CoA. It has two fates when converted to Acetyl CoA depending on the energy state: the Kreb's Cycle to generate ATP or lipogenesis (Bauman et al., 1972). Propionate is most important gluconeogenic precursor but the capacity of the liver is dependent on the supply of propionate (Drackley et al., 2001). Armentano et al. (1991) showed in feed restricted goats that the conversion of propionate

to glucose in the liver was decreased. Butyrate is heavily oxidized in the portal-drained viscera (90%) and produces β-hydroxybutyrate (BHB,(Huntington, 1990).

Non esterified fatty acids are produced as a result of lipolysis. Ruminants have higher levels of NEFA during periods of fasting (DiMarco et al., 1981). During periods of NEBAL or feed restriction, increased plasma NEFA concentrations are a glucose sparing mechanism for cows in lactation (Wheelock et al., 2010). However; during heat stress, studies have shown no increase in NEFA concentrations during this time (Calamari et al., 2013; Rhoads et al., 2009; Shwartz et al., 2009; Wheelock et al., 2010). This is surprising as heat stressed cows have increased acute stress hormones (cortisol, norepinephrine, and epinephrine; (Collier et al., 2005) which help in mobilization of adipose tissue and shows with a decrease in body weight. It must be noted that heat stressed non-lactating cows differ in metabolic profiles from lactating cows on a lowered plane of nutrition which was described by Rhoads et al. (2009).

Ketones such as acetoacetate and BHB are byproducts of β-oxidation when the mitochondrion is overloaded with acetyl-CoA. Acetoacetate is formed from two acetyl-CoA while BHB requires three. Blood ketone levels decrease when ambient temperature increases (Dale and Brody, 1954).

Protein

Although not the largest contributor to gluconeogenic substrates, proteins can be catabolized to amino acids to meet the energy needs. Alanine and glutamine make the greatest contribution (40-60%) to the glucose pool (Bergman and Heitmann, 1978). During fasting, peripheral tissue releases branched chain amino acids that are used as ketogenic precursors to support maintenance requirements or plasma proteins (Bergman, 1986). Plasma urea nitrogen

(PUN) has two sources: rumen ammonia or deamination of amino acids from the liver (Bernabucci et al., 2010). The increase in biomarkers of muscle catabolism during HS has been shown in pigs (Hall et al., 1980), lactating cows (Wheelock et al., 2010), and heifers (Ronchi et al., 1999). Some other indicators that are better at assessing skeletal muscle origin are either 3-methyl-histidine or creatine (Schneider et al., 1988). Milk proteins are negatively affected by HS (Rhoads et al., 2009; Shwartz et al., 2009). Hu et al. (2016) demonstrated *in vivo* that HS induced HSP70 decrease casein in mammary epithelial cells which is a plausible explanation for decreased milk protein synthesis.

Heat Stress Abatement

Genetics

An increase in performance production, especially lactating dairy cows, has led to an increase in metabolic heat production, which makes cattle more susceptible to HS (Renaudeau et al., 2012). There are two strategies that can be used to identify specific breeds: 1) identify phenotypes that will meet current and future market specifications and 2) select animals that are proven to have met the current market specifications (Gaughan et al., 2009). The genetic variation between cattle breeds is substantial for heat tolerance (Legates et al., 1991). When breeds are crossed, the lactating cattle have better resistance to heat but have lower milk production (Collier et al., 2006a).

One gene that plays a role in heat tolerance is the slick hair gene (Olson et al., 2003). The color and density of the hair coat affect thermoregulation (radiation), the airflow over the skin, and the number of sweat glands (Collier et al., 2008). Klungland and Våge (2003) noted the importance of hair color while Olson et al. (2003) included hair length and density for qualities

in determining thermoregulation. Holstein cows with altered hair coats have lower respiration rates and vagina temperature while having higher sweating rates (Dikmen et al., 2008).

For the lactating cow, Collier et al. (2008) identified genetic pathways for physiological processes involved in thermotolerance. The major changes in gene expression listed are heat shock transcription factor 1 (HSF1), heat shock proteins (HSP), immune system, and post-absorptive metabolism (Collier et al., 2008). Genes will favor decreased beta oxidation, increased glucose, and amino acid oxidation. An example is HSP70 on casein production. Casein in mammary epithelial cells decreased when exposed to HSP (Hu et al., 2016). Cell survival is correlated with elevated levels of HSP (Pirkkala et al., 2001).

Facilities

Modifying the environment in which cattle are confined to is an effective way to reduce the severity of HS. The most effective cooling systems take into account solar radiation, ambient temperature, and relative humidity and therefore utilize the thermoregulatory mechanisms previously described (conduction, convection, evaporation, and radiation) to achieve this (Collier et al., 2006a; Fuquay, 1981; West, 2003). The desired effect of creating an environment that has a lower ambient temperature so that the core body temperature is able to exchange heat (VanBaale et al., 2006).

Shade is the most economically and implemented source of protection from solar radiation to reduce heat stress (West, 2003). In lactating dairy cows, shades were able to increase milk yield, decrease respiration rate as well as rectal temperatures (Roman-Ponce et al., 1977).

Fans circulate air around animals and help exchange heat via convection. Kibler and Brody (1954) reported that fans lowered the skin temperature of the animal which decreases the

heat exchange via radiation, conduction, and sweating. This limits their use to only when the air temperature is less than the cattle's core body temperature. Fans can be equipped to have low pressure water injected into the air stream with curtains to prevent mobilization of cooled air that may be effected by natural air currents (Armstrong, 1994). This method has been noted to have an increase in milk production up to 2 kg/day when compared with fans and spray to shade (Igono et al., 1992).

Feedline soakers take advantage of evaporation being the most effective heat exchange mechanism. They are successful in arid as well as humid climates (Armstrong, 1994; Strickland et al., 1989). Shultz was able to show that by implementing feed soakers, producers were able to increase not only milk production but also reproduction efficiency of cows.

Facility design can greatly improve performance during HS. Economic inputs and resources are often the limiting factor when running cooling mechanisms. While facilities can greatly mitigate the negative effects of HS, other strategies can compensate for deficits. Nutritional alterations to diets could reduce the metabolic heat produced during HS.

Nutritional Strategies

Product formation (e.g. milk) accounts for the largest amount of heat energy generated (52.9%) of total heat production in cattle (Coppock, 1985). This is evident in lactating cows with high producing cows (31.6 kg/d) having a 48.5% higher heat production in comparison to non-lactating dry cows (Purwanto et al., 1990). Maust et al. (1972) demonstrated that early lactation cows were less sensitive to HS when compared to mid and late lactation cows.

Fiber

High fiber diets have been shown to increase production of heat. Coppock and West (1986) reported that as the percentage of hay decreased by 50%, the efficiency of metabolizable energy to milk increased by 11% in cows subjected to HS. One VFA associated with high fiber diets is acetate. Acetate produces more endogenous heat than propionate which is associated with a high concentrate feed (West, 1999). One common practice is to create a high fermentable carbohydrate diet to increase energy intake but this predisposes cattle to rumen acidosis (West, 2003). West (1999) states maintaining acid detergent fiber (ADF) and neutral detergent fiber (NDF) be higher than 18% and 28% on dry matter for the diet.

Protein

A reduction in feed intake has been shown to put cattle undergoing HS in a negative nitrogen balance (Kamal and Johnson, 1970; O'Brien et al., 2010; Ronchi et al., 1999; Shwartz et al., 2009). Cows fed 16.1% crude protein with low degradability had greater milk yield than cows fed 18.5% crude protein with medium degradability (Huber et al., 1994).

Supplementation with methionine and lysine have been reported to have positive effects. This is credited to these amino acids being rate limiting (Nichols et al., 1998). Methionine improved milk production when fed to cows subjected to HS (Nichols et al., 1998). Some research has shown supplementation of high levels of rumen-undegradable protein during hot climates didn't enhance performance of lactating cows (Maianti et al., 2001). However, Calamari et al. (2013) observed a positive effect on milk yield when feeding a similar diet that consisted of rumen undegradable protein with fatty acids and glycol to dairy cows.

Huber et al. (1994) reported a decrease in feed intake and milk production because of the additional energy required to metabolize the protein to urea for excretion when feeding excess

rumen degradable protein. One way to bypass this is to improve the quality and use rumen ungradable protein.

Fat

Adding fat to the diet increases the energy of ration without compromising on the metabolic heat unlike adding starch. While there are benefits to adding fat, the current literature has conflicting results. Supplementing a high-fat diet to crossbred steers under heat stress showed lower body temperature (O'kelly, 1987). Knapp and Grummer (1991) reported no significant difference with diet x environment interaction with a 5% increase in supplement fat diets.

While there are benefits to adding dietary fats to compensate for energy, these feed sources are vulnerable to oxidation which negatively impact the rumen function and intestinal wall. Major sources of dietary fat are distiller grains (wet and dry), soybean extract, fish meal, corn meal, brewer grains, and cottonseed meal. When not stabilized, these feed sources contribute to the generation of free radicals in the animal (Andrews and Vazquez-Anon, 2006). Oxidative stress induced by HS is difficult to study in cattle because of the decrease in feed intake which means most work is done in pigs and poultry. Effects of oxidized fats fed to animals led to decreases in performance, gut integrity, and compromises the immune responses (Cabel et al., 1988; Dibner et al., 1996). Vázquez-Añón and Jenkins (2007) reported reduced microbial protein metabolism that was measured with lower digestion of crude protein, lower nitrogen yield, and increased biohydrogenation when feeding oxidized fats to lactating dairy cows. Implementing antioxidants into diets improved lactation performance with increases in dry matter intake, fat-corrected milk, and milk fat yield (Vázquez-Añón et al., 2008).

Water

Water is essential for thermoregulatory requirement and homeostasis for cattle, especially in heat stress. One response to heat stress by cattle is to increase water consumption (McDowell, 1972). Beede and Collier (1986) list the three forms of water supply (metabolic water, water in ingested feed, and drinking water) with drinking water being the most significant. Water consumption is correlated to feed intake and milk yield (Murphy et al., 1983). This is shown in lactating dairy cows that are undergoing acute HS. Collier et al. (2018) summarized that higher producing cows have a reduced feed intake and also experience a decrease in water intake with cows producing less than 25 kg/day of milk have the opposite effect. Chronic exposure to HS; however, was reported to increase water intake compared to cows in thermoneutral conditions (Collier et al., 2018). Supplying cattle with cooled water during HS showed increased weight gain in beef cattle (Ittner et al., 1951) and improved milk yield (Milam et al., 1986). There is a difference between species as breeds adapt to their environment under various conditions (Koga et al., 2002).

Minerals and Vitamins

Mineral intake is reduced by heat stress because of the reduced feed intake. The leaky gut theory may be involved due to the decrease in surface area. Epithelial cells have decreased viability (Vergauwen et al., 2015) from oxidative stress which is induced by HS (Liu et al., 2016). Supplementation must be able to cover the turnover as well as to buffer diet and environment effects (Calamari et al., 2007). The following trace minerals have shown potential

immunologic benefits when supplemented to cattle during stress: selenium, copper, zinc, and chromium.

Selenium (Se) is vital for lots of components of the immune system but it is a major component of glutathione peroxidase, thus having a role in antioxidant properties such as removing hydrogen peroxide. A deficiency in Se can incite oxidative stress (Chaudiere et al., 1984). In lactating cows, Smith et al. (Smith et al., 1984) found a decrease in diseases and infections when feeding elevated Se levels.

Copper (Cu) is involved with adaptive and innate immunity. Deficiency in Cu can be caused by either low intake of Cu or hi intake of iron or molybdenum (Suttle, 1986). Spears (2000) summarized several studies which reported reduced antibody and cytokine production from mononuclear cells when cattle are Cu deficient. Supplementing Cu had variable effects with the humoral response by increasing antibody titers in stressed cattle (Ward and Spears, 1999).

Chromium (Cr) is an essential mineral for glucose and insulin metabolism since it acts on peripheral tissue by enhancing the responsiveness and sensitivity to insulin (Morris et al., 1993). Spears (2000) reviewed a number of studies with adding Cr to the diet and indicated that it may improve cell-mediated and humoral immune response. One study suggested that Cr is beneficial by relieving stress-induced immunosuppression (Burton et al., 1993).

Zinc (Zn) is a cofactor in a large portion of enzymes and having a deficiency can affect the immune function, tissue regeneration, protein synthesis, and inflammatory responses (Erickson et al., 2000). Spears (2000) outlines that Zn deficiency has a small impact on ruminant immune function, but that providing additional Zn has some benefits.

Electrolytes are in high demand during heat stress. Bovine sweat is composed of the cation potassium and its secretion is enhanced during HS. Potassium supplementation in the form of potassium salts has shown an improvement in feed intake and milk production when fed during heat stress (Sanchez et al., 1994). Sodium bicarbonate is excreted to counter respiratory alkalosis to balance pH. Collier et al. (2006a) states feeding sodium bicarbonate to reduce rumen acidosis is necessary to increase the buffering capacity of the rumen. Supplementing diets with sodium bicarbonate was reported to improve feed intake and milk production (Schneider et al., 1984).

Vitamins play a vital role in the performance and immune function of cattle. Vitamins A, C, and E are supplemented during HS because of their anti-stress effect (West, 1999). When combined with trace elements, vitamins A and E have been noted to improve mammary health by decreasing mammary gland infections (Chew, 1987; Sordillo et al., 1997). This was supported by Khorsandi et al. (2016) with observations of milk somatic cell score being reduced with supplementation of trace minerals and vitamins.

Oxygen free radicals have the potential to be increased during HS (Calamari et al., 1999) and thus cause oxidative stress (Bernabucci et al., 2002). Supplementation with vitamin C and E are relevant because of their antioxidant capacity. Brigelius and Traber (1999) reported α-tocopherol showing beneficial effects with diseases linked to oxidative stress. When a mix of vitamin E and Se were added to the diet, some alleviation of HS was reported for night time feeding (Tahmasbi et al., 2012).

Vitamin B is produced in the rumen by microbes. Supplementation during HS has been recommended due to the decrease in rumination time, feed intake, and change in metabolic demands (Rhoads et al., 2009). Some vitamin B derivatives such as niacin, thiamin, and biotin

have shown benefits in ruminants under normal conditions (Schwab et al., 2005; Shaver and Bal, 2000; Zimmerly and Weiss, 2001). Recent studies with supplementation of rumen-protected niacin showed inconsistency with effects. Niacin was shown to positive effects on lactation performance for milk yield (Guo et al., 2017) and increased milk fat (Pineda et al., 2016; Zimbelman et al., 2013). Other studies have shown no effect on milk production but had some alleviation of HS (Rungruang et al., 2014; Zimbelman et al., 2010). Rungruang et al. (2014) detected a decrease in skin temperature and increased water intake. Zimbelman et al. (2010) concluded that niacin increased evaporative heat loss and decreased vaginal temperatures.

Pre- and Probiotics

Yeast are members of the fungi family and a eukaryote, single-celled organism. They are able to survive in the rumen and influence the microbes when active by scavenging oxygen and producing bacterial growth factors (Kung et al., 1997). Commercially available yeast products are seeing an increase in demand due to the changes in regulation of antibiotic use in animal production. Yeast express pre- and probiotic properties by increasing nutrient digestibility and improving feed efficiency (Huber et al., 1994).

Fermented feed additives such as the yeast culture alter microbiota. Yeast cultures come in a variety of ways: live or inactivated yeast cells, the culture medium, and metabolic by-products (Linn and Raeth-Knight, 2006). They serve as prebiotics by being a source of growth factors and vitamins for rumen microbes (Opsi et al., 2012). They also act as probiotics by promoting the growth, rumen health, and production of cattle (Nocek and Kautz, 2006).

During HS, the negative impacts of depressed feed intake and increased maintenance energy inhibit production. Using feed additives with yeast blends to improve production have

mixed results. Positive results for lactating cattle such as improved milk yield (Bruno et al., 2009), increased DMI (Moallem et al., 2009), and feed efficiency (Schingoethe et al., 2004) have been noted during hyperthermia. However, one research group noted no significant changes with feed intake or production but only slightly reduced body temperature (Shwartz et al., 2009).

Recently, it has been noted that cattle need to be preconditioned prior to exposure to heat stress to fully benefit from supplementation. Several studies have shown that feeding an immunomodulator, OmniGen-AF (Phibro Animal Health, Teaneck, NJ), decreased observable responses of HS on a feeding period more than 1 month (Fabris et al., 2017; Hall et al., 2018; Leiva et al., 2017). Fabris et al. (2017) exposed dry-off cows to different environmental conditions and reported cows fed OmniGen-AF and were cooled had an increase in milk yield, gestation length, and calf weight. Although this feed additive alters metabolic and immune responses in cattle, there has been no impact on feedlot performance or carcass qualities (Buntyn et al., 2016).

CONCLUSION

Mitigating HS through the utilization of feed additives during stressful times would be beneficial to producers who lack the resources to minimize heat gain and maximize heat loss. Cattle experience significant levels of heat stress when exposed to weather above body temperature and elevated humidity. The influence of yeast culture has been thoroughly researched in terms of production but little has been shown terms of metabolic profile of blood parameters in vitro. The objective of these studies was to establish the efficacy of feed additives as a way to alleviate HS in cattle.

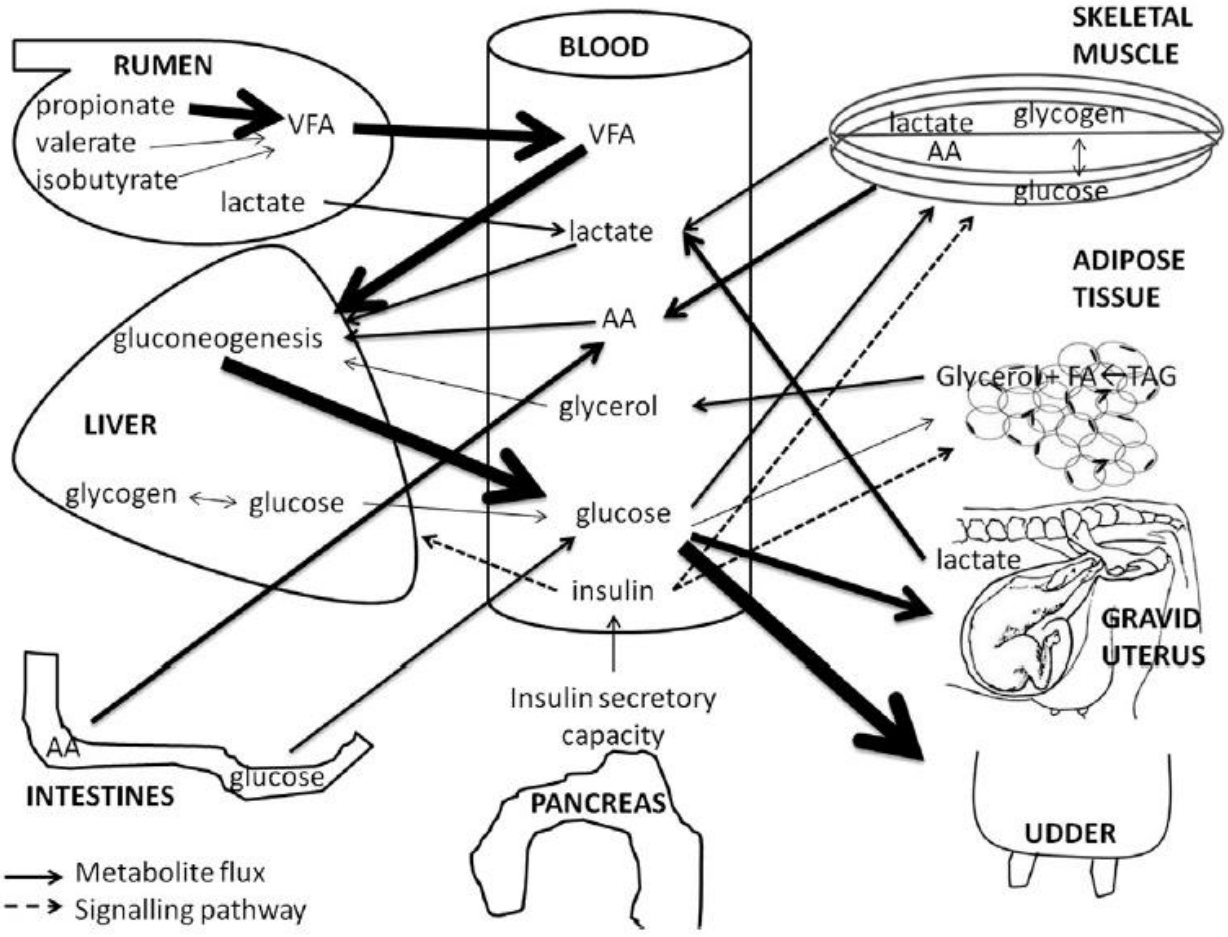
Figure 1.1 Temperature Humidity Index for Dairy Cows (Zimbelman et al., 2009)

Themperature		% Relative Humidity																					
°F	°C	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
72	22.0	64	65	65	65	66	66	67	67	67	68	68	69	69	69	70	70	70	71	71	72	72
73	23.0	65	65	66	66	66	67	67	68	68	68	69	69	70	70	71	71	71	72	72	73	73
74	23.5	65	66	66	67	67	67	68	68	69	69	70	70	70	71	71	72	72	73	73	74	74
75	24.0	66	66	67	67	68	68	68	69	69	70	70	71	71	72	72	73	73	74	74	75	75
76	24.5	66	67	67	68	68	69	69	70	70	71	71	72	72	73	73	74	74	75	75	76	76
77	25.0	67	67	68	68	69	69	70	70	71	71	72	72	73	73	74	74	75	75	76	76	77
78	25.5	67	68	68	69	69	70	70	71	71	72	73	73	74	74	75	75	76	76	77	77	78
79	26.0	67	68	69	69	70	70	71	71	72	73	73	74	74	75	76	76	77	77	78	78	79
80	26.5	68	69	69	70	70	71	72	72	73	73	74	75	75	76	76	77	78	78	79	79	80
81	27.0	68	69	70	70	71	72	72	73	73	74	75	75	76	77	77	78	78	79	80	80	81
82	28.0	69	69	70	71	71	72	73	73	74	75	75	76	77	77	78	79	79	80	81	81	82
83	28.5	69	70	71	71	72	73	73	74	75	75	76	77	78	78	79	80	80	81	82	82	83
84	29.0	70	70	71	72	73	73	74	75	75	76	77	78	78	79	80	80	81	82	83	83	84
85	29.5	70	71	72	72	73	74	75	75	76	77	78	78	79	80	81	81	82	83	84	84	85
86	30.0	71	71	72	73	74	74	75	76	77	78	78	79	80	81	81	82	83	84	84	85	86
87	30.5	71	72	73	73	74	75	76	77	77	78	79	80	81	81	82	83	84	85	85	86	87
88	31.0	72	72	73	74	75	76	76	77	78	79	80	81	81	82	83	84	85	86	86	87	88
89	31.5	72	73	74	75	75	76	77	78	79	80	80	81	82	83	84	85	86	86	87	88	89
90	32.0	72	73	74	75	76	77	78	79	79	80	81	82	83	84	85	86	86	87	88	89	90
91	33.0	73	74	75	76	76	77	78	79	80	81	82	83	84	85	86	86	87	88	89	90	91
92	33.5	73	74	75	76	77	78	79	80	81	82	83	84	85	85	86	87	88	89	90	91	92
93	34.0	74	75	76	77	78	79	80	80	81	82	83	85	85	86	87	88	89	90	91	92	93
94	34.5	74	75	76	77	78	79	80	81	82	83	84	86	86	87	88	89	90	91	92	93	94
95	35.0	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95
96	35.5	75	76	77	78	79	80	81	82	83	85	86	87	88	89	90	91	92	93	94	95	96
97	36.0	76	77	78	79	80	81	82	83	84	85	86	87	88	89	91	92	93	94	95	96	97
98	36.5	76	77	78	80	80	82	83	83	85	86	87	88	89	90	91	92	93	94	95	96	98
99	37.0	76	78	79	80	81	82	83	84	85	87	88	89	90	91	92	93	94	95	96	98	99
100	38.0	77	78	79	81	82	83	84	85	86	87	88	90	91	92	93	94	95	96	98	99	100
101	38.5	77	79	80	81	82	83	84	86	87	88	89	90	92	93	94	95	96	98	99	100	101
102	39.0	78	79	80	82	83	84	85	86	87	89	90	91	92	94	95	96	97	98	100	101	102
103	39.5	78	79	81	82	83	84	86	87	88	89	91	92	93	94	96	97	98	99	101	102	103
104	40.0	79	80	81	83	84	85	86	88	89	90	91	93	94	95	96	98	99	100	101	103	104
105	40.5	79	80	82	83	84	86	87	88	89	91	92	93	95	96	97	99	100	101	102	103	105
106	41.0	80	81	82	84	85	87	88	89	90	91	93	94	95	97	98	99	101	102	103	104	106
107	41.5	80	81	83	84	85	87	88	89	91	92	94	95	96	98	99	100	102	103	104	106	107
108	42.0	81	82	83	85	86	88	89	90	92	93	94	96	97	98	100	101	103	104	105	107	108
109	43.0	81	82	84	85	87	89	89	91	92	94	95	96	98	99	101	102	103	105	106	108	109
110	43.5	81	83	84	86	87	89	90	91	93	94	96	97	99	100	101	103	104	106	107	109	110
111	44.0	82	83	85	86	88	90	91	92	94	95	96	98	99	101	102	104	105	107	108	110	111
112	44.5	82	84	85	87	88	90	91	93	94	96	97	99	100	102	103	105	106	108	109	111	112
113	45.0	83	84	86	87	89	91	92	93	95	96	98	99	101	102	104	105	107	108	110	111	113
114	45.5	83	85	86	88	89	92	92	94	96	97	99	100	102	103	105	106	108	109	111	112	114
115	46.0	84	85	87	88	90	92	93	95	96	98	99	101	102	104	106	107	109	110	112	113	115
116	46.5	84	86	87	89	90	93	94	95	97	98	100	102	103	105	106	108	110	111	113	114	116
117	47.0	85	86	88	89	91	93	94	96	98	99	101	102	104	106	107	109	111	112	114	115	117
118	48.0	85	87	88	90	92	94	95	97	98	100	102	103	105	106	108	110	111	113	115	116	118
119	48.5	85	87	89	90	92	94	96	87	99	101	102	104	106	107	109	111	112	114	116	117	119
120	49.0	86	88	89	91	93	95	96	98	100	101	103	105	106	108	110	111	113	115	117	118	120

- Stress Threshold. Respiration rate exceeds 60 BPM. Milk yield losses begin. Reproduction losses detectable. Rectal temperature exceeds 38.5˚C (101.3˚F).
- Mild-Moderate Stress. Respiration rate exceeds 75 BPM. Rectal Temperature exceeds 39˚C (102.2˚F).

- Moderate-Severe Stress. Respiration rate exceeds 85 BPM. Rectal Temperature exceeds 40˚C (104˚F).
- Severe Stress. Respiration rate exceeds 120-140 BPM. Rectal Temperature exceeds 41˚C (106˚F).

Fig. 1.2 Overview of glucose metabolism. (De Koster and Opsomer, 2013)



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Appendix A

Responses and adaptations in crossbred Hereford steers exposed to heat stress

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ABSTRACT

Heat stress (HS) is a prominent issue globally, especially in the Southwestern United States, on feedlots where cattle are exposed to radiant heat and have reduced mechanisms to cool themselves. Feed supplements, such as Beef Abate (BA), are commercialized to help mitigate the effects of hyperthermia on growth development by improving metabolic and immune functions. Twelve crossbred Hereford steers (250 ± 100 kg) were randomly assigned to one of two dietary groups: control group (CON) received 56.7 g of placebo/hd/day; BAF group received 56.7 g of BA/hd/day. Steers were randomly assigned to one of two tie stall rooms with 6 steers per room and 3 steers per treatment/room. Rooms were exposed to cyclical daily temperature humidity index (THI) of 70 - 81 and 27 – 39 for heat-stress (HS) and the thermoneutral (TN) rooms respectively for a total of 15 days. To account for confounding alterations in HS-associated changes in feed intake, each TN steer was pair-fed daily to the intake level of its HS weight-paired cohort with the adjustment to feed offered to TN steers made 24 h after the intakes of HS steers were measured. Blood samples were collected twice daily via indwelling jugular catheter

at 700 and 1500 h. Serum BHBA, glucose, cortisol, triacylglycerides (TAG), non-esterified fatty acids (NEFA), and insulin were analyzed twice daily. Respiration rate, rectal temperature, and skin temperature were measured daily at 1500 h. Average daily water consumption and average daily weight gain were calculated at the end of the experimental period. Heat stress increased water consumption ($P<0.001$), respiration rate ($P<0.001$), and skin temperature ($P<0.001$) and tended to increase rectal temperature ($P<0.06$). Supplementation with BA tended to reduced rectal temperatures ($P<0.06$) in heat stressed cattle. Exposure to HS lowered serum glucose ($P<0.01$) and insulin ($P<0.01$) while increasing NEFAS ($P<0.01$) and TAG ($P<0.01$). Supplementation with BA lowered TAG ($P<0.05$) and glucose ($P<0.05$). Heat stress and BA supplementation had no effect on serum cortisol levels. Results of this study suggest that heat stress exposure for 15 days had performance and metabolic impacts in crossbred Hereford steers. Supplementation with the dietary feed additive BA alleviated some of the daily metabolic effects associated with heat exposure.

INTRODUCTION

Environmental factors, such as HS, influence productivity and efficiency in livestock across the globe. Compared to other mammals, cattle cannot dissipate their heat load very effectively. Therefore, temperatures that exceed the thermal neutral zone have been shown to be detrimental in growth, reproduction, immune function, and ultimately on carcass value and quality (Mader, 2003). Cattle do not sweat effectively and rely on respiration to cool themselves. A compounding factor on top of climatic conditions is the fermentation process within the rumen that generates additional heat in which the cattle need to dissipate. HS reduces feed intake which contributes to cattle being in negative energy balance. Cattle under HS display the different

metabolic profiles (i.e., elevated NEFA levels) of an animal on a decreased plane of nutrition (Wheelock et al., 2010). Additionally, increased core body temperatures during HS results in altered endocrine profiles (Collier et al., 2008).

Feed additives have been shown to alleviate the negative impact that is experienced by livestock cattle during periods of heat stress. Supplementation with dietary fats (O'kelly, 1987), cation-anion supplements (Sanchez et al., 1994), and vitamins (Muller et al., 1986) have been shown to have positive performance effects in heat stressed cattle. Other feed supplements and blends that are commercialized to promote metabolic and immune functions during periods of heat stress could also be beneficial during periods of intense heat.

The objective of this study was to evaluate HS tolerance and the dietary feed additive in crossbred Hereford steers during a 15-d period utilizing environmental chamber.

MATERIALS AND METHODS

The study protocol and procedures in regards to the animals were reviewed and approved in accordance with the University of Arizona Institutional Animal Care and Use Committee. Twelve crossbred Hereford steers (250 ± 100 kg) were randomly assigned to individual tie stalls in 1 of 2 environmental chambers at the University of Arizona's William J. Parker Agriculture Research Complex (Tucson, AZ). Throughout the study, steers were fed twice daily at 0600 and 1600 h according to its dietary group: CON received 56.7 g of placebo/hd/day and BA received 56.7 g of BA/hd/day. An 86% concentrate diet mostly composed of steam-flaked corn and alfalfa hay formulated to meet or exceed National Research Council recommendations was used to feed steers (Table 2.1). Refusals were removed and weighed at 0530 daily. Feed intake was calculated daily. The steers were subject to a 14-d period of acclimation under ambient temperature conditions. After the acclimation period, steers were exposed to either a TN

environment (cyclical daily THI 27-39) or HS conditions (cyclical daily THI 70-81) for 15 days (Figure 1). Each TN steer was pair-fed daily to the intake level of its HS weighted cohort with the adjustment made 24 h after the intakes of the HS steers were measured.

Indwelling jugular catheters were surgically inserted into steers to facilitate the acquisition of blood samples. Catheters were replaced after 7 d and inserted in the opposite jugular vein from the initial. Catheters were flushed with 10 mL saline with heparin (100 USP/mL) twice daily. Blood samples were collected twice daily at 0700 and 1500 h. Samples were collected in BD vacutainer tubes (BD Vacutainer, Franklin Lakes, NJ). Serum was obtained from each blood sample by centrifugation at 1500 x g for 15 min at 4℃ and stored at -40℃ until assayed. Serum samples were analyzed for beta-hydoxybutyric acid (BHBA), glucose, triacylglycerides, and non-esterified fatty acids (NEFAs) by EIA kits. Serum cortisol and insulin were analyzed by ELISA test kits.

Performance parameters such as respiration rate, rectal temperature, and skin temperature were recorded daily at 1500 h. Respiration rate was measured by counting flank movements for 60 s. Rectal temperatures were measured using a standard digital thermometer (GLA M700 Digital Thermometer, San Luis Obispo, CA). Skin temperatures were measured at the tail head, rump, and shoulder by shaving a patch of skin and using an infrared temperature gun (Raynger, Raytek MX, Fluke Corporation, Everett, WA). Average daily water consumption and average daily weight gain were calculated at the end of the experimental trial.

Performance parameters and blood data were analyzed as a 2x2 factorial design using the PROC MIXED (SAS Institute 9.4). Independent variables include treatment, day, environment (temp) and their respective interactions. When significant effects were observed ($P<0.05$), differences between the means were evaluated.

RESULTS AND DISCUSSION

At the end of the 15-d HS or TN exposure periods, steers weights were similar ($P \geq 0.124$) between treatments (Table 2.2). As expected, water intake and average daily intake was higher and lower respectively for steers in the HS group compared to the TN group ($P < 0.01$; data not shown). Intake, however, was corrected daily (pair feeding) utilizing the amount consumed in the HS steers to adjust intake of the TN pair steer. Skin temperature and respiration rates were higher for HS steers compared to the TN independent of dietary treatment (Table 2.2). Rectal temperature; however, was neither affected by environment (HS vs. TN) nor by dietary treatment (Table 2.2). In ruminants, short-term heat acclimation is characterized by responses initiated to compensate for the increased HS before permanent acclimation can be obtained. Increased heat dissipation (primarily through evaporative heat loss), reduced feed intake, and increased water intake are examples of the short-term heat acclimation response (Gaughan et al., 2009).

Metabolic parameters are presented in Table 2.3 and Figures 2.1-2.5. Serum concentrations of insulin ($P = 0.003$) and glucose ($P < 0.001$) were lower for HS steers while serum NEFA ($P = 0.0156$) concentrations increased in HS steers (Figures 2.1, 2.3 and 2.4). Triacylglycerols concentrations tended to increase for steers under HS conditions ($P = 0.0618$, Figure 2.2). Serum concentrations of cortisol (Figure 2.5) and BHBA (not shown) were not affected by HS exposure. Cortisol levels are elevated during acute HS and decrease during chronic heat stress and may be associated with metabolic adaptations (Collier et al., 1982). Over the length of the experimental period supplementation with Beef Abate affected serum concentrations of HS steers (Figures 2.1-2.4). These responses tended to occur after days 9–10 and again in days 12–14. Beef cattle are less sensitive than dairy cattle to heat stress due to the

overall decrease in endogenous heat production (lower plane of production, reduced heat increment of feeding, etc. (Bernabucci et al., 2010). Variability in the length of acclimation period ranges from 9 d for Angus and Charolais to 14 d for Polled Hereford (Hereford and Santa Gertrudis had intermediate values (12 d); which coincided with some of the treatment responses in the present study.

IMPLICATIONS

Information on the impacts of short-term exposure of beef cattle to high THI conditions are limited in the literature. In this study, crossbred Hereford steers showed marginal negative effects in performance and biochemical parameters after a 15-d exposure to medium-to-high THI conditions. Supplementation with the feed additive blend product Beef Abate improved, delayed, or tended to improve some of the negative impacts of HS during specific time points during the experimental period suggesting potential benefits in commercial situations. Further studies are needed under higher THI condition or during longer periods of exposure to better examine the full impact of HS on feedlot steers and the benefits of supplementation under these conditions.

Table 2.1. Ingredient composition of diets (CON and BA)

Item	**% of DM**
Ingredient	
Alfalfa hay (ground)	13.7%
Corn (steam flake)	73.2%
Mineral	2.1%
Molasses	6.3%
Soybean Meal	3.8%
Urea	0.9%

Table 2.2. Effects of Environment and Treatment on Performance Parameters in Beef Steers

	Heat Stress (HS)		Thermoneutral (TN)			*P* value	
Parameter	Control	Treatment	Control	Treatment	SEM	Environment	Treatment x Environment
Rectal Temp (°C)	38.57	38.62	38.57	38.47	0.04	NS	NS
Skin Temp (°C)	37.18	37.15	32.34	31.34	0.12	<0.0001	<0.0001
Respiration (Breaths/min)	51.1	49	27.6	27.6	0.91	<0.0001	NS
Weight Change (kg/day)	0.82	0.62	1.23	3.02	0.82	NS	NS
Average Daily Intake (kg/day)	7.01	7.56	8.39	8.62	0.16	<0.0001	NS

Table 2.3. Effects of Beef Abate on metabolic parameters

	Control		Beef Abate			*P*-value		
Parameter	TN[1]	HS[2]	TN	HS	Mean SEM	ENV	TRT	TRT x ENV
NEFA[3] (µmol/L)	127.11	160.32	116.96	125.96	8.61	0.0156	0.0106	0.1599
TAG[4] (mg/dL)	12.78	16.50	12.18	11.07	1.47	0.4023	0.0742	0.1398
Insulin (ng/mL)	2.5	1.65	2.43	1.60	0.27	0.0135	0.8122	0.9694
Glucose (mg/dL)	76.25	74.65	81.55	75.01	1.52	0.0288	0.1015	0.1446
Cortisol (ng/mL)	6.08	6.25	6.77	6.34	6.36	0.8868	0.6813	0.7549
BHBA[5] (mM)	474.71	561.91	528.45	479.00	29.50	0.54	0.6344	0.0492

[1]=Thermoneutral
[2]=Heat Stress
[3]=Non esterified fatty acids
[4]=Triacylglycerol
[5]=β-hydroxybutyrate

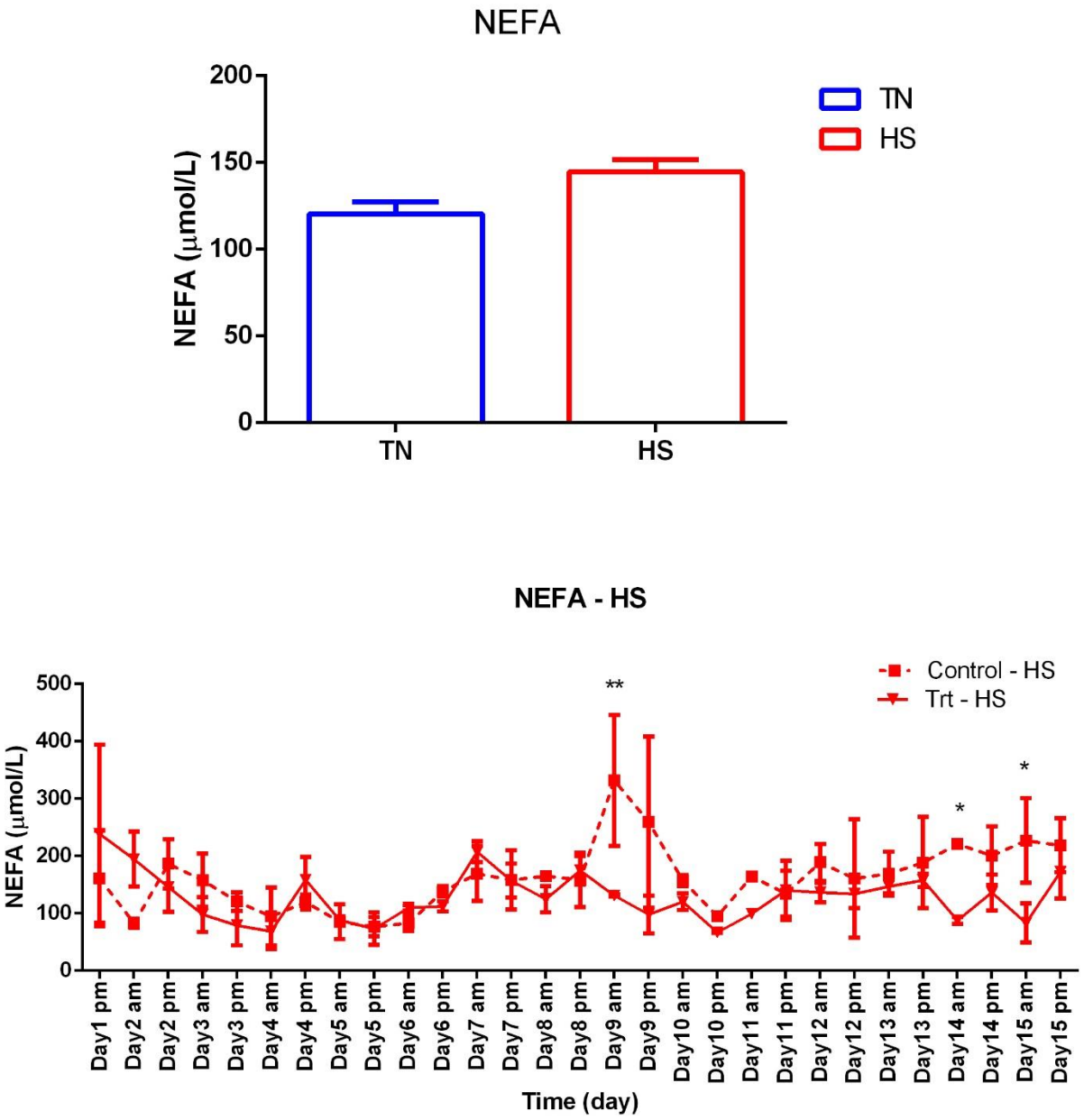

Figure 2.1. Serum NEFA concentrations (µmol/L) in CON and TRT steers during TN and HS (ENV, *P*=0.015).

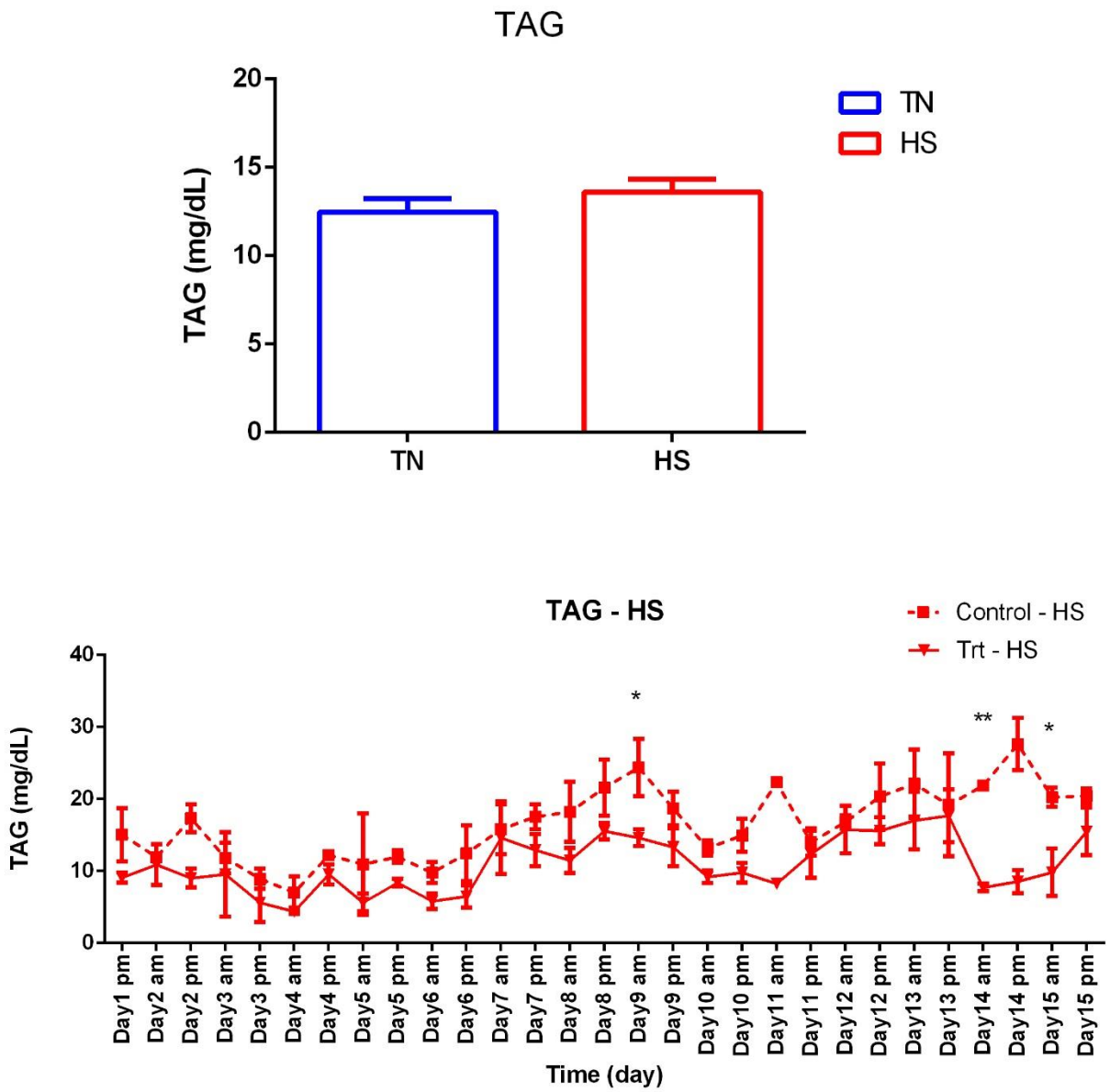

Figure 2.2. Serum TAG concentrations (mg/dL) in CON and TRT steers during TN and HS (No significant difference).

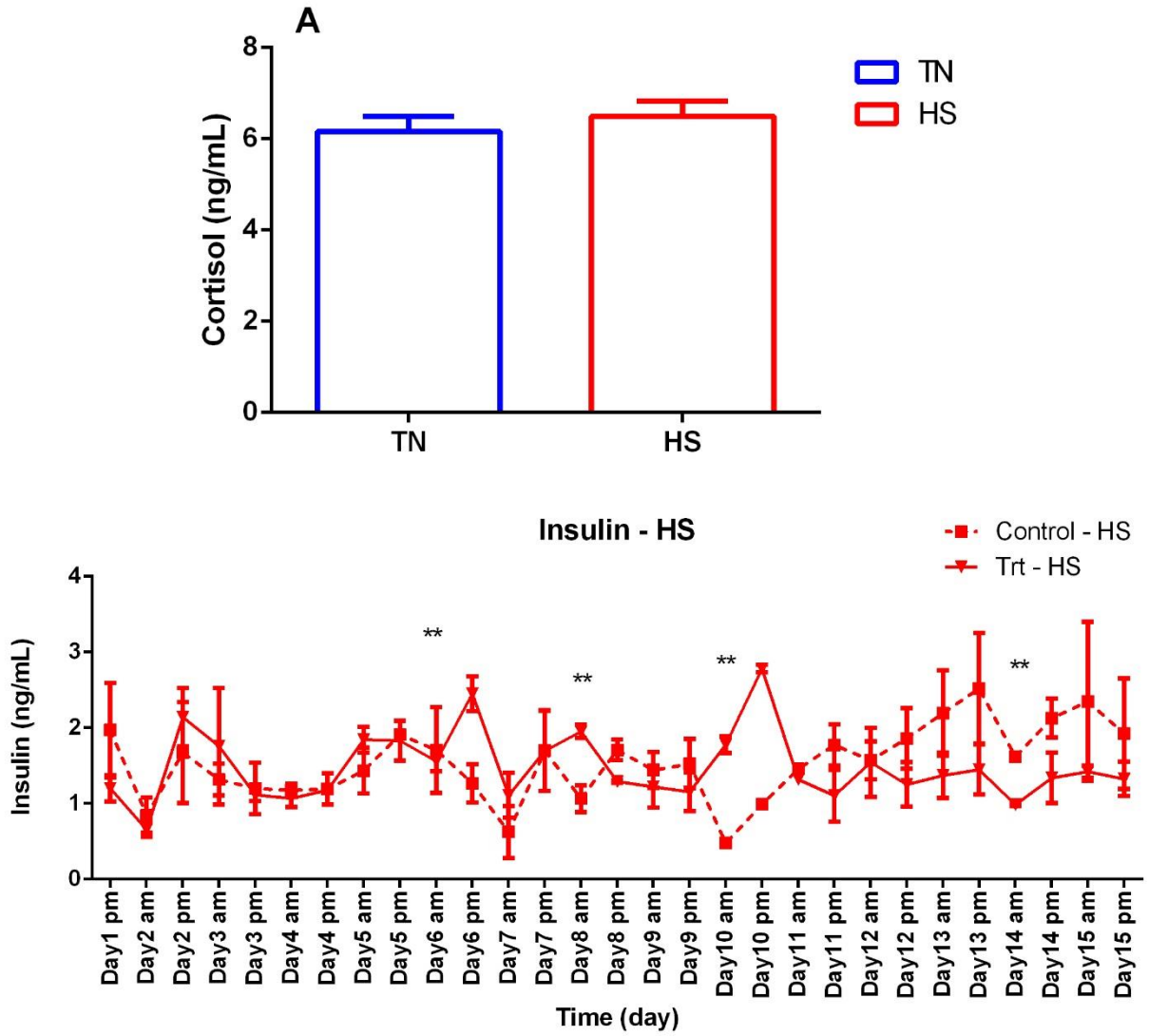

Figure 2.3. Serum insulin concentrations (ng/mL) in CON and TRT steers during TN and HS (ENV, *P*=0.013).

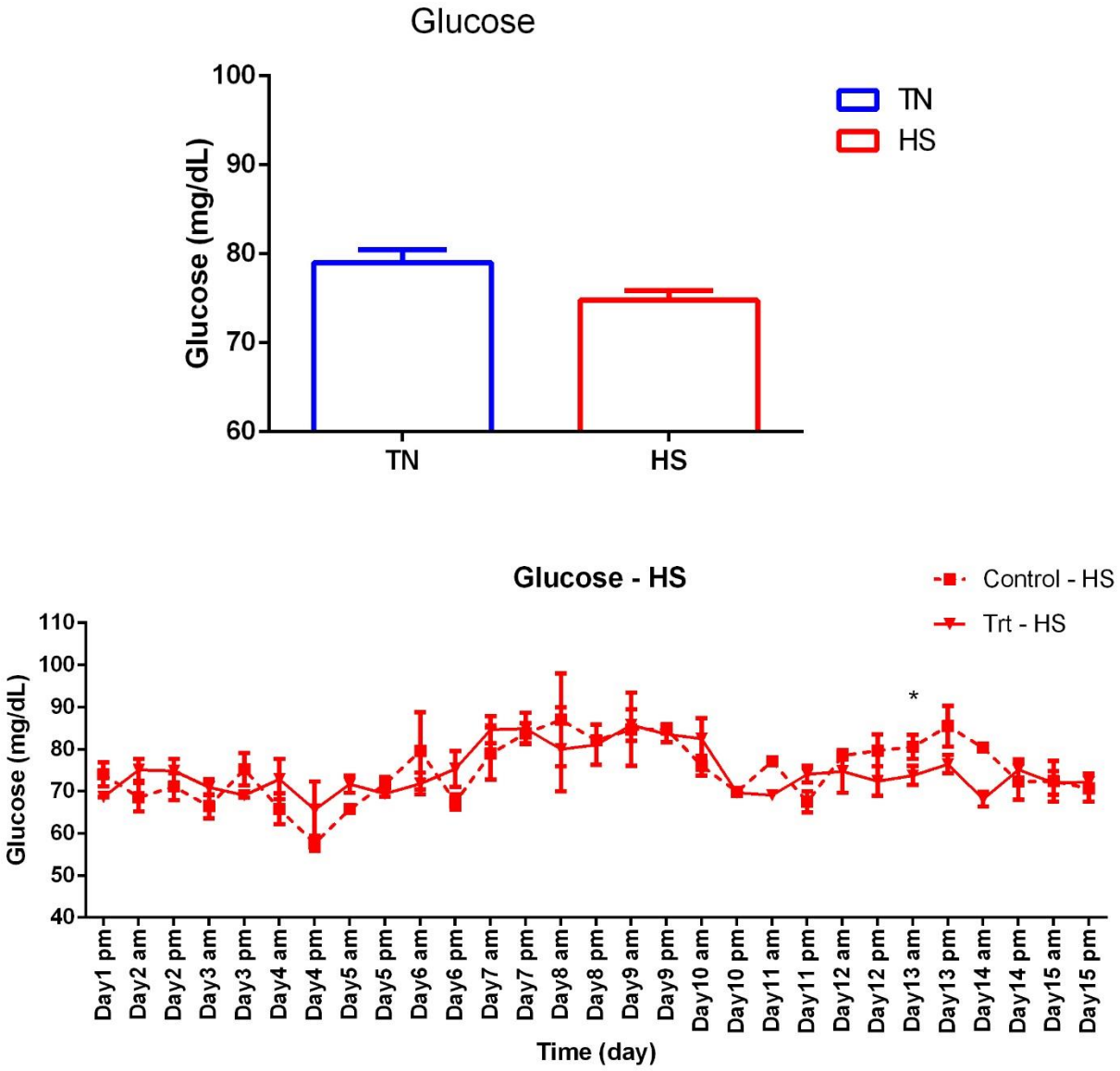

Figure 2.4. Serum glucose concentrations (mg/dL) in CON and TRT steers during TN and HS (ENV, *P*=0.028).

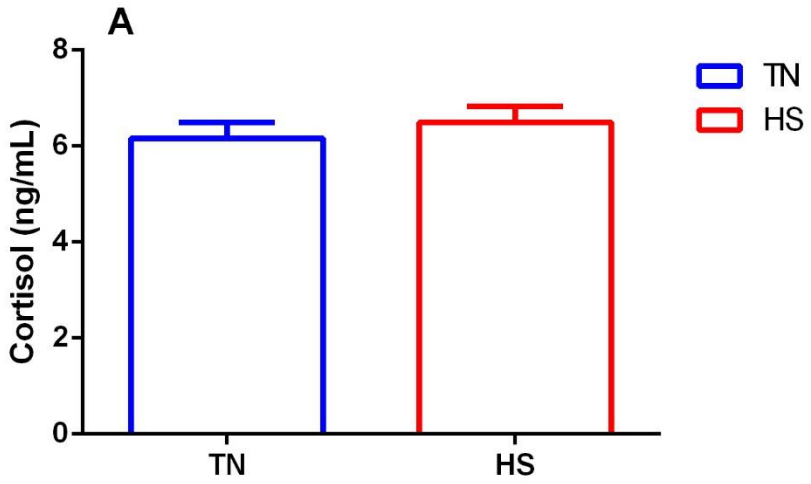

Figure 2.5. The effect of HS or TN on serum cortisol (ng/mL) in steers (*P*=0.344).

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Appendix B

Evaluation of lactating Holstein cows during heat stress in response to a dietary feed additive in mid lactation

Pending publication in the Journal of Dairy Science

ABSTRACT

Heat stress **(HS)** has detrimental effects on lactating cattle especially when they are in a negative energy balance. Feed additives have been shown to mitigate the effects of HS by improving metabolic and immune function. The objective of this study was to evaluate the effect of feeding a dietary supplement (PMI Nutritional Additives, Arden Hills, MN) on the HS response in multi-parturient dairy cows in mid lactation. Two pens of cows at a commercial dairy were fed either control **(CON)** or additive **(YB)** at approximately 56.5 kg/pen per d for two weeks prior to arrival. Study cows (n=12) were balanced in days in milk **(DIM)**, milk production, and parity (111.91±4.85 d, 33.67±0.96 kg/d, and 2.25±0.18). Cows (6 TRT and 6 CON) were randomly selected and housed in environmentally controlled chambers for 18 d and fed appropriate diet. Cows were subjected to 7 d of thermoneutral **(TN)** conditions, 7 d of HS, and 4 d of recovery **(REC)** under TN conditions. Dry matter intake **(DMI)**, milk production from AM and PM milkings, and milk composition were measured daily. Rectal temperature **(RT)** and respiration rate (RR) were measured at peak temperature daily. Blood samples were collected once daily at 1500 h following catheterization on d 4 of TN to d 4 of REC. Serum samples were analyzed for glucose, insulin, blood urea nitrogen **(BUN)**, β-hydroxybutyrate **(BHB)**, and non-esterified fatty acids **(NEFA)**. Results were analyzed using repeated measures in the PROC MIXED of SAS. HS increased RT (P<0.0001), RR (P<0.0001), BUN (P<0.0001), insulin (P=0.04), neutrophil (P=0.009), and water intake (P=0.0005). HS decreased lymphocyte

(*P*=0.0008), DMI (*P*=0.0007), energy corrected milk (**ECM**, *P*=0.01), and 4% fat corrected milk (**FCM**, *P*=0.02). YB decreased the feed efficiency ratio (*P*=0.03). YB had no effect on blood parameters. There was a treatment x environment interaction with cows fed YB having lower feed efficiency (*P*=0.02) during peak thermal loads than CON. Results of this study suggest that HS exposure had performance and metabolic impacts in mid lactation cows. Supplementation with YB alleviated some of the performance effects associated with HS.

INTRODUCTION

HS is a costly factor to the dairy industry (St-Pierre et al., 2003) as it changes the livestock production system due to increasing climate variability (Thornton, 2010). Physiological responses occur when the temperature-humidity index (THI) exceeds 68 or when the ambient temperature exceeds 32.2˚C (Allen et al., 2015). Measurable factors that are negatively affected by heat stress are milk production, dry matter intake, growth, and health disorders (West, 1999). It has been shown that milk yield is affected by HS through independent mechanisms of reduced nutrient intake (Wheelock et al., 2010).

Increasing the energy density of the diet from carbohydrates sources to fatty acid sources are common methods for feeding heat stressed animals but increase the chances of rumen acidosis per Kadzere et al. (2002). Using supplemental dietary additives have been shown to stabilize the rumen and increase post-rumen nutrient flow (Erasmus et al., 1992) in non-stressed cows; however, Shwartz et al (2009) reported no effect of a yeast culture on mitigating the effects of heat stress on lactating cows. The feed additive used in this study was a proprietary phytogenic and specialty yeast blend (PMI Nutritional Additives, Arden Hills, MN) that has been shown to alter metabolic parameters in growing cattle (Diaz et al., 2018). Proven feed additives

have shown increased immune function in lactating dairy cows (Brandão et al., 2016) by altering cortisol responses in supplemented cows (Hall et al., 2018).

We hypothesized that supplementing with the YB would increase energy availability and thus reduce the negative effect of the heat load on production measures. The study objectives were to evaluate the effects of the dietary YB on body, production, and metabolic parameters in heat stressed lactating cows.

MATERIALS AND METHODS

This study was conducted at the Agricultural Research Complex (ARC) at the University of Arizona (Tucson, AZ). The protocol was reviewed and approved by the University of Arizona Institutional Animal Care and Use Committee. It occurred in two phases: on-farm and on-site.

The on-farm phase consisted of feeding one 500 cow pen and monitoring a control pen of the same number of cows at a dairy in Stanfield, AZ. Treatment cows were given the feed additive in the TMR at 56.5 kg/pen and received it for 2 weeks. Previous research has shown that there may be a cell-mediated response in the rumen and that requires time to see a response during heat stress (Hall et al., 2018). After the 2-week period, 6 treatment cows and 6 control cows were shipped to the ARC for the on-site phase with no health issues (rumen acidosis, ketosis, lameness, mastitis, metritis).

Upon arrival, twelve multiparous Holstein cows producing 33.67 ± 0.96 kg of milk/d, lactation (2.25 ± 0.18), and stage of lactation (111.92 ± 4.85 DIM) were weighed and randomly assigned to individual tie stalls in one of two environmental chambers. Both chambers housed 6 cows (3 control and 3 treatment). Chambers operated on the same environment throughout the study. There were 4 periods: acclimation (4 days), thermal neutral (TN, 7 days), heat stress (HS,7 days), and recovery period (4 days) (Figure 3.1). The acclimation period and TN period were set

on the same environmental cycle. The TN environment was set at a minimum temperature of 21.16˚C, a maximum of 21.48˚C, and an average of 21.39˚C. The relative humidity (RH) had a minimum of 28.32%, a maximum of 36.73%, and an average of 32.30%. The temperature-humidity index (THI) had a minimum of 65.54, a maximum of 66.16, and an average of 65.84 (Figure 3.2). The HS period had a minimum temperature of 25.40˚C, a maximum of 34.89˚C, and an average of 30.09˚C. The RH had a minimum of 23.40%, a maximum of 36.48%, and an average of 30.88%. The THI had a minimum of 70.68, a maximum of 80.70, and an average of 75.46 (Figure 3.3). The Recovery period had a minimum temperature of 21.11˚C, a maximum of 21.43˚C, and an average of 21.38˚C. The RH had a minimum of 40.46%, a maximum of 50.93%, and an average of 45.93%. The THI had a minimum of 66.39, a maximum of 66.99, and an average of 66.78 (Figure 3.4). The THI of 68 identifies as the threshold for HS in lactating dairy cows (Collier et al., 2011).

THI values were calculated using the average temperature and relative humidity obtained from the data logger. THI was defined by the formula (Ravagnolo et al., 2000):

$$THI = ((1.8 \times T_{db}) + 32) - (0.55\text{-}0.0055 \times RH) \times (1.8 \times T_{db} - 26)$$

Where: T_{db} = dry bulb temperature (˚C), RH = relative humidity percentage.

The diet was an alfalfa based TMR that was balanced to be consistent with the green chop based TMR on the commercial dairy. Grab samples were collected once every 3 days when a new batch of feed was mixed. Alfalfa was added to the TMR pre-mix and was stored at 4 ^{o}C. Samples were analyzed by Dairy Nutrition Services INC (Chandler, AZ) by wet chemistry.

Feeding and milking were done twice daily at 0530 and 1730 h. The CON cows were fed the base TMR. The YB cows were fed the TMR plus 113.4 g of YB mixed. Orts were removed and weighed in the morning prior to feeding. The feed efficiency was determined by using 4%

fat corrected milk (FCM) per kilogram of DM consumed for each cow in each treatment group. Water consumption was recorded daily from the water meters after the AM feeding. Milk weights were recorded daily and a daily milk sample was taken from the AM milk. Milk samples were individually refrigerated with a preservative (Bronopol tablet, D&F CON Systems, San Ramon, CA) at 4℃. Samples were analyzed for fat, lactose, protein, somatic cell count (SCC), and solids-not-fats (SNF) by Arizona DHIA (Tempe, AZ). Body weights were recorded twice during the study: once during HS and at the beginning of REC.

Physiological measurements such as respiration rate and rectal temperature were recorded for each cow once daily at 1400 h. Respiration rate was recorded as breaths per minute. It was calculated by counting the flank movements for 15s and multiplying by 4. Rectal temperature was measured using a Cooper TM99A thermometer (Cooper-Atkins, Middlefield, CT). Cows that exceeded 40.5℃ were removed from the chamber and were cooled with water until a rectal temperature of 38.3℃. Vaginal temperatures were recorded with HOBO® U12 stainless steel temperature data loggers (Onset Computer Corp., Bourne, MA) in 5 minutes increments. Blank controlled internal drug releasing devices (Eazi-Breed™ CIDR®; Zoetis, Parsippany-Troy Hills, NJ) were used to hold the HOBO in the vagina. The cows were fit with this apparatus on d 1 for the duration of the study. CIDR placement was monitored and were refitted if they were expelled from the vagina.

Blood was collected via indwelling jugular catheters that were surgically inserted into cows on day 4 and 5. Blood was collected at 0900 h from day 5 to 18. Catheters were flushed before sampling and once at 1500 h with heparinized saline (100 USP/mL). The first 6 mL of fluid was discarded to eliminate heparin. Two 12 mL syringes with a 22-gauge needle were used to draw blood and were transferred to BD Vacutainer tubes (BD, Franklin Lakes, NJ): sodium

heparin and blank. Samples were chilled for one hour at 4℃. Serum and plasma were collected after centrifuging samples at 1,500 x g for 15 min at 4℃ and stored at -80℃ until analysis. Additional blood samples for white blood cell differentials were collected in BD Vacutainer tubes with EDTA. Differentials were run by Antech Diagnostics (Phoenix, AZ).

Serum β-hydroxybutyrate (BHB) was determined by a colorimetric kit (β-hydroxybutyrate (Ketone Body); Cayman Chemical, Ann Arbor,MI). Serum blood urea nitrogen (BUN) was determined using a colorimetric kit (DetectX Urea Nitrogen; Arbor Assays, Ann Arbor, MI). Serum glucose was measured using a colorimetric assay (Glucose Oxidase; Pointe Scientific Inc., Canton, MI). Serum non-esterified fatty acid (NEFA) was determined enzymatically through a commercial kit (Wako NEFA-HR(2); Wako Chemicals USA, Richmond, VA). Serum insulin was determined using an enzyme linked immunosorbent assay (ELISA) kit (Bovine Insulin, ELISA kit; ALPCO, Salem, NH).

Plasma cortisol was assessed using an enzyme immunoassay (EIA) kit (Cortisol Parameter Assay; R&D Systems Inc., Minneapolis, MN). Plasma Tumor Necrosis Factor-α (TNF-α) was measured using an ELISA kit (Bovine TNF-alpha ELISA; RayBiotech Life, Norcross, GA).

Metabolic Rate Study

Tissues biopsies were done on both skeletal muscle and mammary gland to determine metabolic rate. The target skeletal muscle was the infraspinatus. Muscle biopsies were done at 0900 h on day 6, 11, 14, 18. The upper shoulder region was shaved and rinsed with betadine and 70% ethanol. 3 mL of 2% Lidocaine HCl (Hospira Inc., Lake Forest, IL) was administered to that region and each cow was given 3 minutes for maximum numbing effect. A small incision with a scalpel blade (size #10) was made. A 18 G x 15 cm quick core biopsy needle with a 20

mm throw length was used to extract the tissue sample. The incision site was sealed with vetbond and allowed to dry before triple antibiotic ointment was applied. A topical antiseptic (Nolvasan) was sprayed to the site. The mammary quadrant of choice was the right rear. Mammary biopsy were performed on day 18 at 0900 h.

Tissue samples were immediately assayed for metabolic activity. Dulbecco's Modified Eagle Medium (DMEM) without phenol red and glucose, 0.1 % (v/v) dimethyl sulfoxide (DMSO), 1% (v/v) penicillin-streptomycin solution, and 4% (v/v) alamarBlue. Cultures were read at 0,1,2, and 4 h with fluorescence excitation wavelengths 530-590 nm. Tissues were removed from the culture and frozen at -80℃ for further analysis.

Mammary Epithelial Cell Study

10 mL of AM milk samples were collected from individual cows on day 6, 11, 15 and 16. Milk samples were collected for both AM and PM milking on day 15 respectively. A drop of milk was added to a slide, smeared, and stained with H&E. The remaining milk sample was inserted into 15 mL centrifuge tubes. Samples were centrifuged at 2500 G at 4℃ for 5 minutes. Liquid was decanted after removing fat film. 1 mL of TRIzol^{TM} LS (Invitrogen, Carlsbad, CA) was added to the vial and the pellet was resuspended. Samples were transferred and stored in 2 mL freezer tubes at -80℃ for further analysis.

Statistical Analysis

Physiological and blood data were analyzed using a PROC MIXED model as a 2 x 2 replicated factorial design with the LSMEANS and PDIFF options within each environmental period as the REPEATED option with day within period as the repeated measure, and effect of the cow was nested within treatment, using a covariant structure. Rectal and vaginal temperatures were averaged per hour by day of trial. Environment, treatment, and environment x

treatments effects were tested by means of the PDIFF option and were declared significant at $P < 0.05$. One cow was removed because of adaptation complications: severe hypophagia and constant standing.

RESULTS AND DISCUSSION

Environmental conditions prior to arrival to ARC were not documented. All cows of the same treatment were housed in the same Saudi style barn cooled using Koral Kool systems and were kept below 72 THI. The recorded environmental conditions for the TN, HS, and REC periods of the study are shown (Figure 3.2). As cows are exposed to conditions above 68 THI, RR exceeds 60 (Berman, 2005) and RT elevates above 38.5ºC (Allen et al., 2015). Due to these differences in parameters, changes in physiology and performance measures are prevalent between environmental groups.

Mean RR and RT in CON and YB fed cows are shown in Table 3.2. There was no difference in treatment for RR and RT. There is conflicting data on the effect of treatment on RT. Baumgard et al. (2011) reported an increase in RT when cows were fed a feed additive during HS. Other studies reported a reduction in RT with supplementation during hyperthermia (Brandão et al., 2016; Fabris et al., 2017). There was an effect of environment ($P<0.0001$) for both these variables as cows exposed to a THI above the threshold increases these parameters. HS cows increased RR (42 breaths/min) and RT (1.32˚C) compared to TN cows which indicates heat stress was achieved.

Feed intake, water intake, milk yield, and components are reported in Table 3.3. Dry matter intake (DMI) increased in both groups as cows adjusted to the facility during the TN period but experienced a slight decrease due to feed heating during 2 days of storage (Figure 3.3). DMI differed between TN and HS ($P=0.0007$). Thermal stress has been well documented in

causing a decrease in DMI and how that drop in DMI may impact milk yield. Previous heat stress research has shown an altered endocrine profile that differs from nutrient restricted cows which affect precursors of milk components, such as glucose (Baumgard et al., 2011; Rhoads et al., 2009; Wheelock et al., 2010). There was no effect of TRT and TRT x ENV for DMI. Schingoethe et al. (2004) had similar findings in that supplementation of a yeast culture had no effect on DMI during the summer. On the contrary, Wiedmeier et al. (1987) suggested that during periods of stress, fungal supplemental products could be effective with increasing digestibility of structural carbohydrates. This is supported by Moallem et al. (2009) using a live yeast supplementation which saw an increase in feed intake and efficiency during the hot season. There was no difference in water intake between treatment groups for each environmental phase (Figure 3.4). Water intake increased during HS from TN (P=0.0005) and decreased during REC from HS (P<0.0001). Murphy et al. (1983) reported similar water intake values in lactating Holstein cows. Cows fed YB had a higher feed efficiency (1.15 vs. 1.34, P=0.05) compared to CON (Figure 3.5). There was also an effect of ENV (P<0.0001) with feed efficiency increasing during HS and decreasing during REC. Improvement in feed efficiency has been reported in hyperthermic conditions with supplementation of feed additives that contained live yeast and yeast culture (Moallem et al., 2009; Schingoethe et al., 2004). BW differed between TRT (P=0.0235) with YB cows having lower BW than CON. There was an effect of ENV (P=0.0103) with BW decreasing during periods of HS. The interaction between ENV x TRT was not significant for BW.

Milk and FCM yield differences weren't detected between CON and YB groups (Figure 3.6). These results are similar to previous studies using feed additives containing yeast cultures (Schingoethe et al., 2004; Soder and Holden, 1999). Other studies have shown an increase in

milk yield with yeast supplementation but it is correlated with greater DMI for ruminants (Stella et al., 2007; Wohlt et al., 1998). Milk yield declined during HS (P=0.002). This decline in milk yield is only partially due to a decrease in DMI which has been shown by Rhoads et al. (2009). FCM differed between environments with TN being more elevated than HS (P=0.02). There was no significant difference in the following milk components: protein percentage, lactose percentage, and SCC. Previous work by Hall et al. (2018) with HS has shown an increase in SCC during the REC but there was no significance observed in this study. The hypothesis is that during heat stress, mammary epithelial cells sluff post HS and contribute to the rise in SCC. Fat percentage had an effect of ENV (P=0.0129). Milk fat percentage had no difference between TN and HS which is surprising while there was fat depression observed during the REC. Rhoads et al. (2009) reported that climate-controlled HS cows don't have reduced milk fat percentages, unlike commercial dairies that frequently experience fat depression during the summer months due to supplementation with high concentrate diets (Kadzere et al., 2002). Not much work has been done during the REC and further research needs to evaluate this in climate controlled cows.

Hormone and metabolite data are presented in Table 3.4. No differences were detected in serum glucose due to TRT, ENV or TRT x ENV (Figure 3.7). This is contrary to other findings (Rhoads et al., 2009; Shwartz et al., 2009). Cowley et al. (2015) had similar results and suggests that the glucose homeostatic regulatory system is able to compensate for the reduction of DMI. No significant differences in serum NEFA for TRT, ENV or TRT x ENV were detected. Serum BHB did not have any significant differences in TRT or TRT x ENV but an effect of ENV was observed (P=0.0009). NEFA and BHB are a significant source of energy for cows in a negative energy balance. BHB decreases during HS according to Dale and Brody (1954) but a decrease during REC which has TN conditions is surprising. This suggests a potential shift in

postabsorptive changes in lipid metabolism since ketones are a by-product of fatty acid oxidation and the cow now favors glucose to lower heat production.

There was a difference in ENV for BUN ($P<0.0001$) and there were no differences in effect for TRT or TRT x ENV. The increase of BUN during HS is similar to previous studies (Shwartz et al., 2009; Wheelock et al., 2010). BUN originates from two sources: inefficient rumen ammonia incorporation or deamination of amino acids as glucose precursors. Erasmus et al. (1992) found that yeast supplemented groups during HS had improved rumen nitrogen balance which supports the increase in urea-nitrogen in circulation. During periods of inadequate nutrition, cows will undergo proteolysis in skeletal muscle to support lactation (Bell, 1995). BUN source could have derived from muscle catabolism; however, BUN isn't a good marker and either 3-methyl-histidine or creatine should be used which increase in HS lactating cows (Kamiya et al., 2006; Schneider et al., 1988).

No difference was detected in serum insulin between TRT groups and TRT x ENV. There was an effect of ENV (Figure 3.8) with insulin increasing during the HS period ($P=0.036$). Elevated insulin levels have been reported likewise during HS periods (Itoh et al., 1998; Wheelock et al., 2010). This helps explain why there is no NEFA response due to insulin's antilipolytic properties (Vernon, 1992). Insulin also stimulates protein synthesis and serves as an antiproteolyic hormone (Allen, 1988) which supports the decrease in BUN.

Plasma cortisol had no effect of TRT and TRT x ENV. As expected, there was a significant impact of plasma cortisol on ENV (Figure 3.9; $P<0.0001$). Plasma cortisol has been noted to have an increase during acute but not chronic HS (Christison and Johnson, 1972). Interestingly, we found no response during the acute phase for acclimation to HS and an elevation during the chronic phase. Alvarez and Johnson (1973) reported cortisol spikes that

ranged from minutes to hours after an immediate insult of heat stress which would be on d 8. During acute heat stress, cows adjust cellular pathways to mitigate the effects of heat stress and maintain homeostasis. This is no longer needed once the acclimated phenotype and cows have reached long term heat acclimation (Collier et al., 2006). This supports the decrease of cortisol during the acclimation period. One possibility is the collection of blood samples in the PM may have missed the spike in cortisol. Another possibility is that although similar THI was used to previous studies conducted on HS, a difference in temperature and humidity could have caused this since there can be the same THI but different values for temperature and humidity.

White blood cell differentials are shown in Table 3.5. Neutrophil count increased during HS (Figure 3.10) with an observable difference with an effect for ENV (P=0.02) but not for TRT and TRT x ENV. Lymphocytes decreased during HS and REC (Figure 3.11; P<0.0001) while having no other differences in TRT and TRT x ENV. Interestingly, there was no difference in the neutrophil to lymphocyte ratio. Total white blood cell count was more elevated during TN and decreased throughout the thermal periods respectively (ENV, P=0.009). The results agree with stress induces neutrophilia and lymphopenia (Calamari et al., 2011; Paape et al., 1973; Wegner et al., 1976).

In conclusion, supplementing mid-lactation Holstein cows with YB beginning 14 days before and during exposure to moderate HS showed an increase in some production responses measured by feed efficiency. Feeding YB; however, did not result in the mitigation of negative physiological responses associated with HS. The mechanism behind the increase in feed efficiency is unknown due to there being no glucose or DMI response to treatment and further research should focus on it.

Environmental Rooms		
Day 1 - 7	Day 8 - 14	Day 15 - 18
Thermoneutral	Heat Stress	Thermoneutral

Figure 3.1. Environmental rooms during the study. Thermoneutral (TN) period ran for the initial 7 days. Heat stress followed TN for 7 days. Recovery period was in TN conditions and ran for 4 days. The total duration was 18 days.

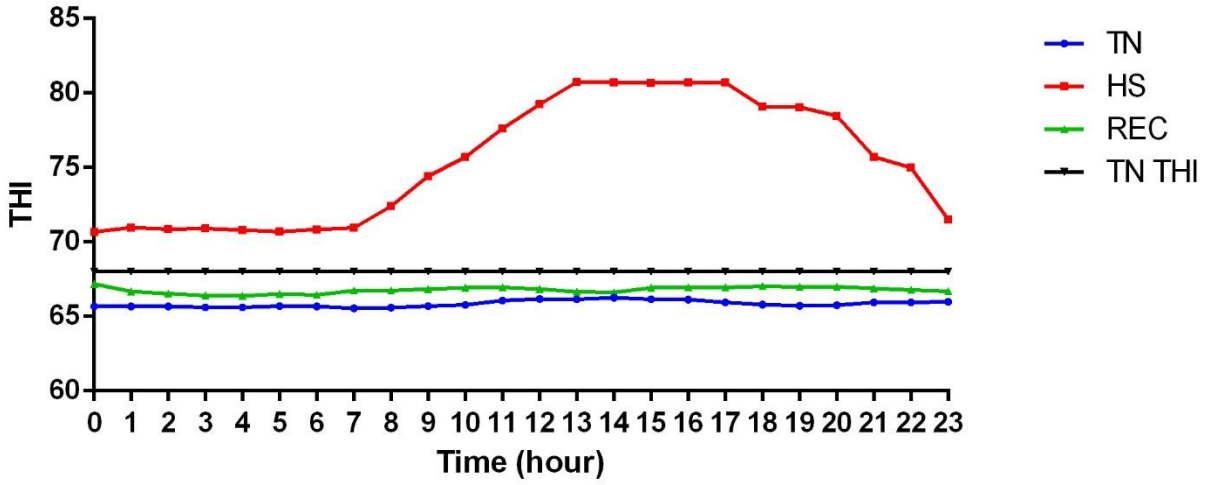

Figure 3.2. Average diurnal patters of temperature humidity index (THI) during different environmental conditions (TN=thermoneutral, HS=heat stress, REC=recovery). The TN THI line is the threshold for HS in lactating dairy cows that has been confirmed by Zimbelman et al. (2009).

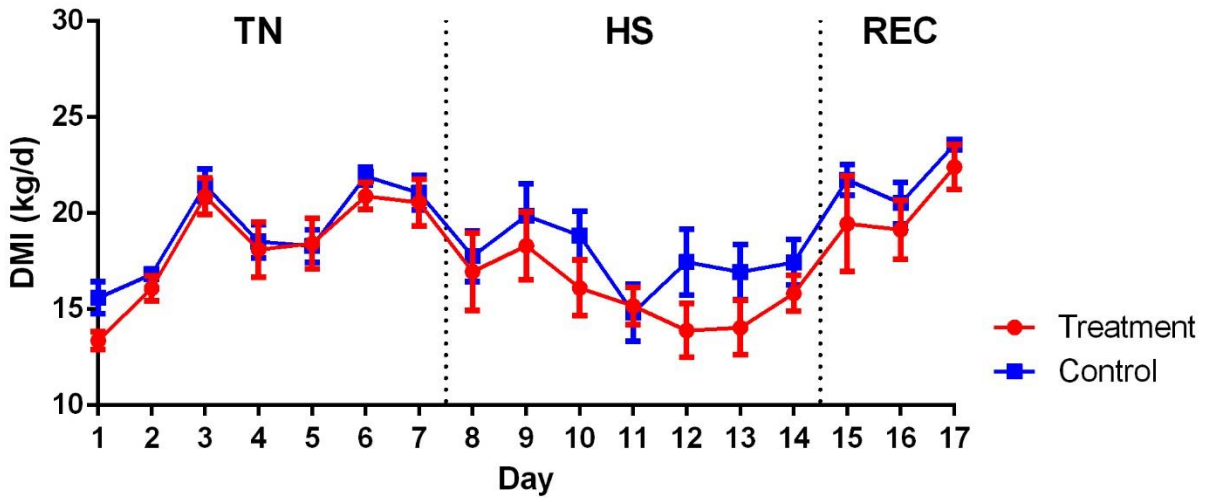

Figure 3.3. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) as well as supplementation of treatment or control on dry matter intake by day (ENV, $P<0.0001$; TN=thermoneutral, HS=heat stress, REC=recovery). Vertical dashed lines separate environmental periods (TN=d 1-7, HS=d 8-14, REC=d 15-17).

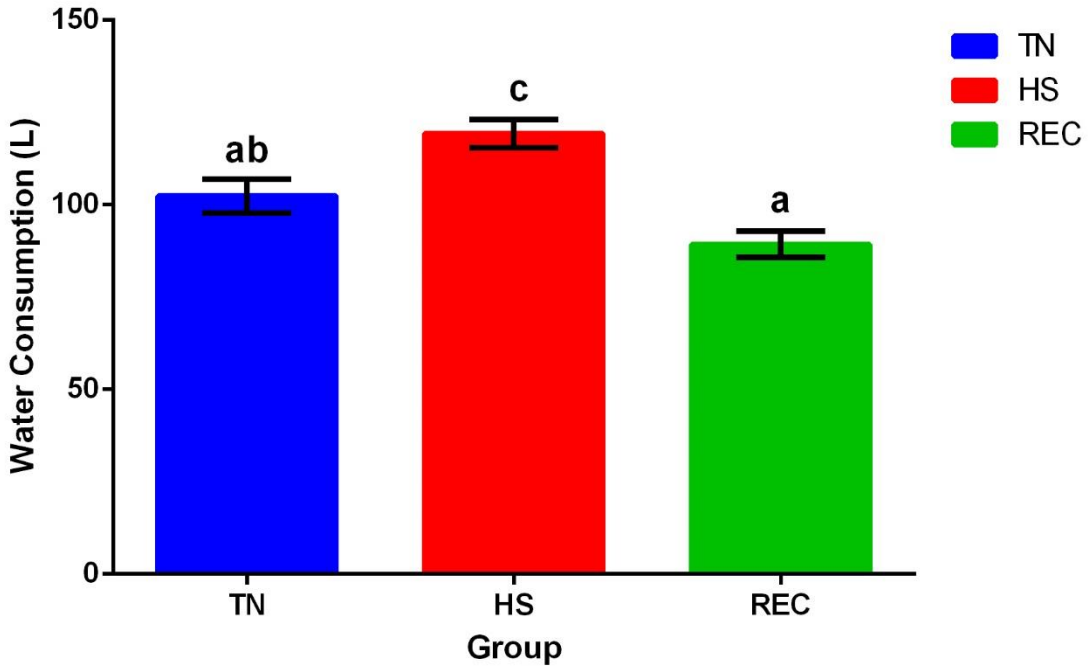

Figure 3.4. Mean daily water consumption between TN (thermoneutral), HS (heat stress), and REC (recovery at thermoneutral) groups (P<0.0001). [a-c]Columns that do not share a superscript differ significantly (P<0.05).

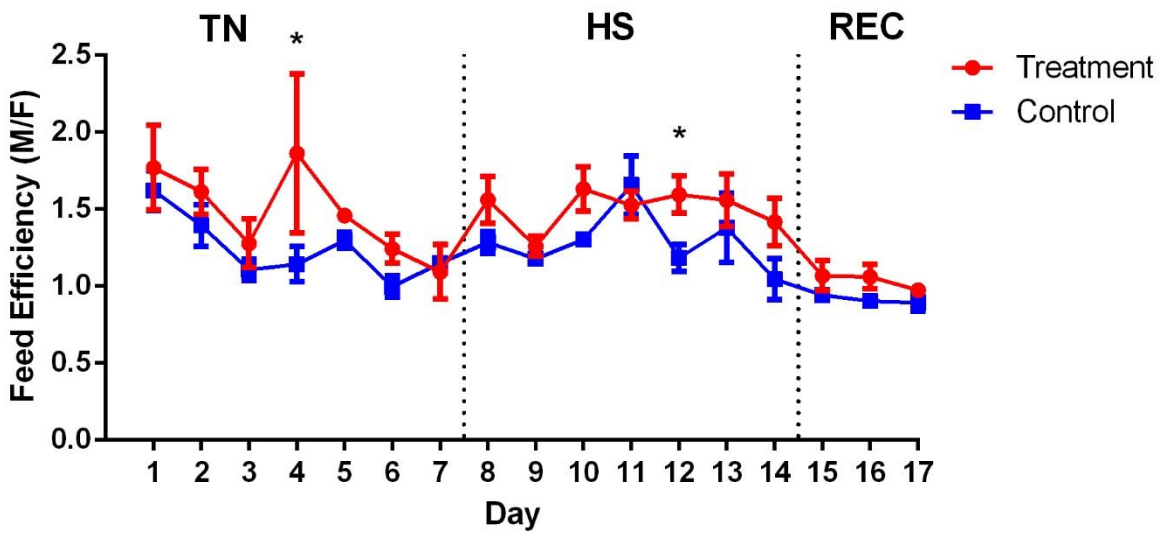

Figure 3.5. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) as well as supplementation of treatment or control on feed efficiency by day (ENV, $P<0.0001$; TRT, $P=0.05$). Vertical dashed lines separate environmental periods (TN=d 1-7, HS=d 8-14, REC=d 15-17). *Indicates significant difference from each treatment group by day for feed efficiency.

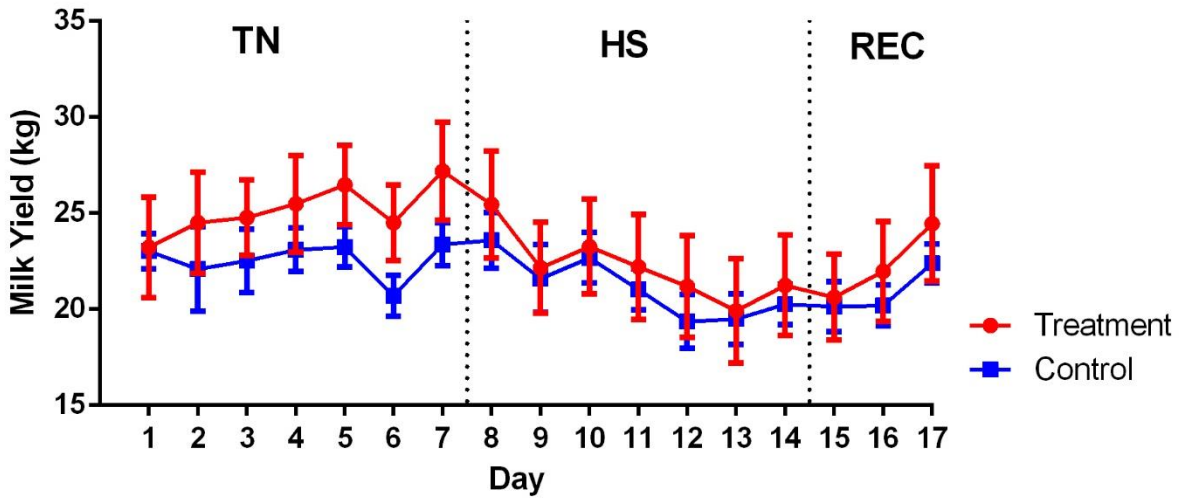

Figure 3.6. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) as well as supplementation of treatment or control on milk yield (kg) by day (ENV, *P*=0.001). Vertical dashed lines separate environmental periods (TN=d 1-7, HS=d 8-14, REC=d 15-17).

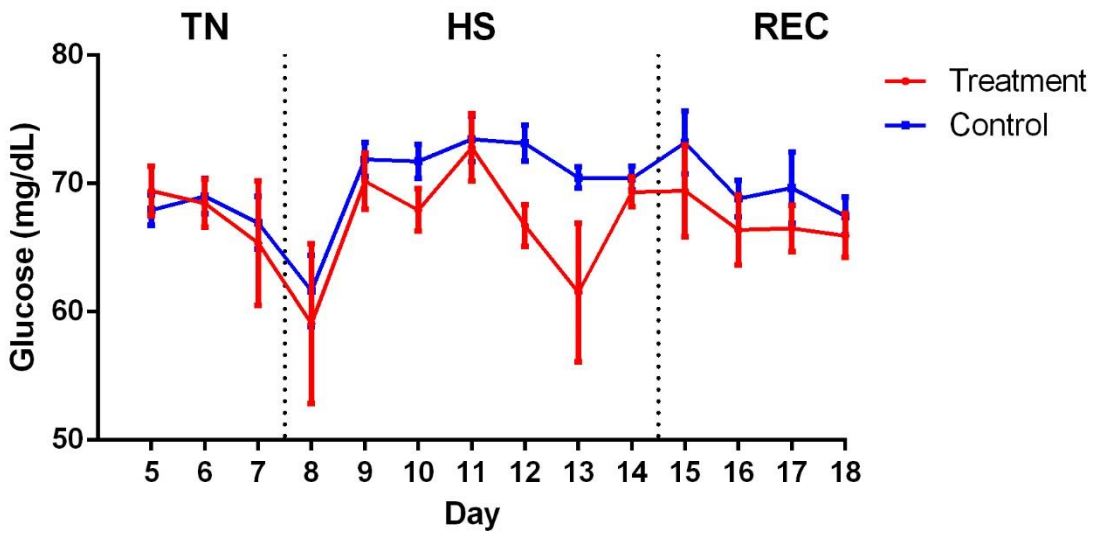

Figure 3.7. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) as well as supplementation of treatment or control on serum glucose (mg/dL) by day (No significant difference). Vertical dashed lines separate environmental periods (TN=d 1-7, HS=d 8-14, REC=d 15-18).

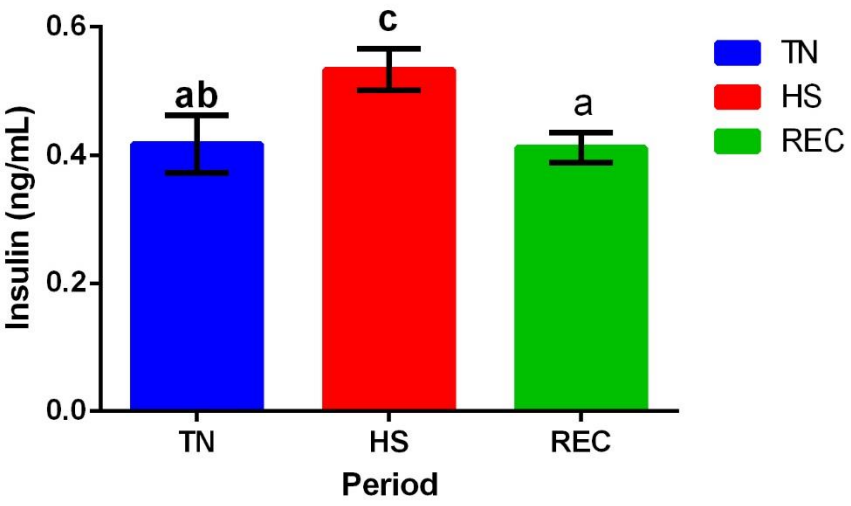

Figure 3.8. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) on serum insulin (ng/mL) with mean of treatment and control (ENV,*P*=0.036). [a-c] Columns that do not share a superscript differ significantly (*P*<0.05).

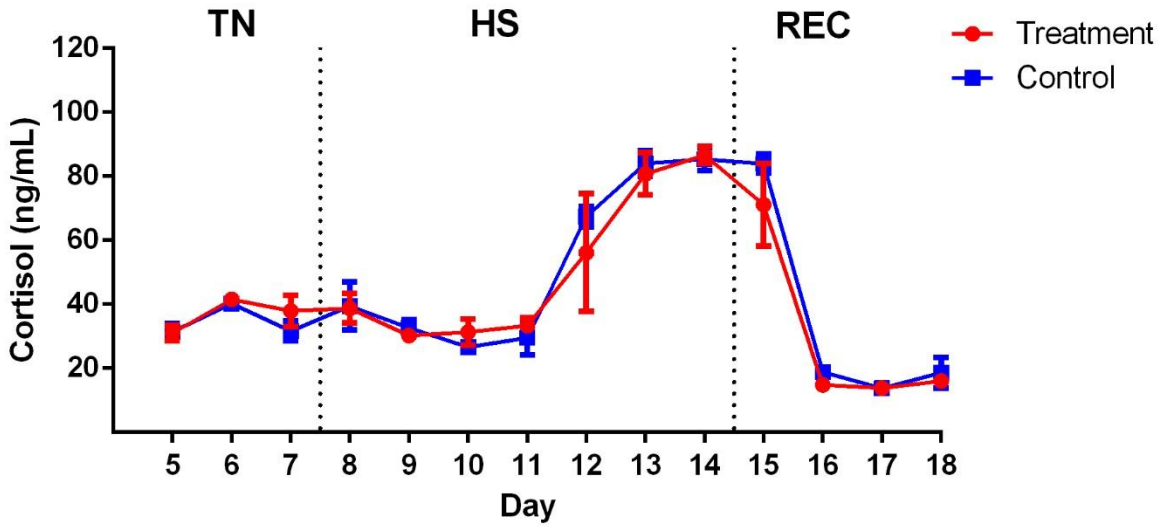

Figure 3.9. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) as well as supplementation of treatment or control on plasma cortisol (ng/mL) by day (ENV, $P<0.0001$). Vertical dashed lines separate environmental periods (TN=d 1-7, HS=d 8-14, REC=d 15-18).

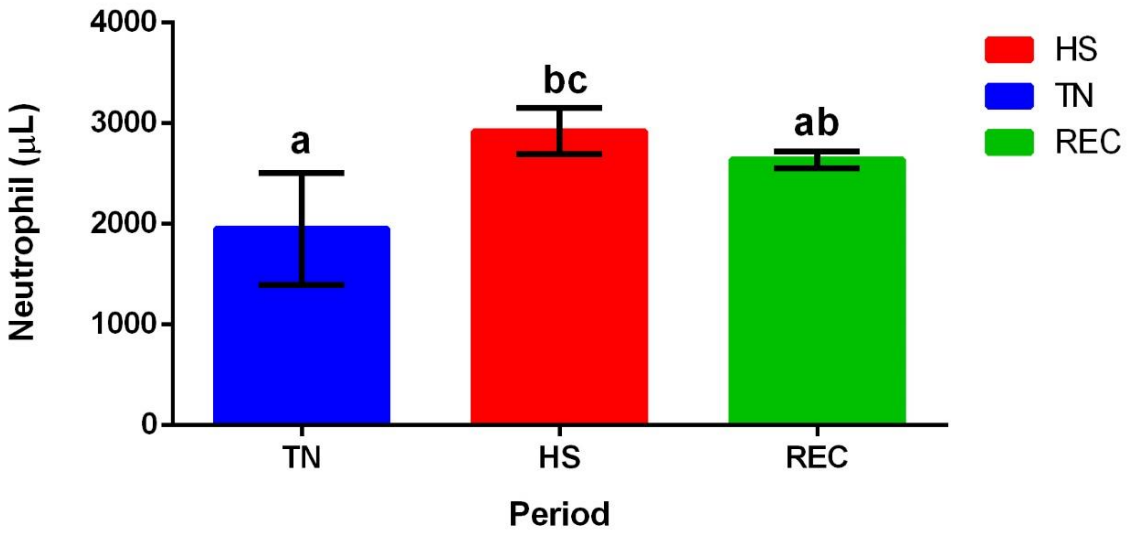

Figure 3.10. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) on neutrophil count (µL) with mean of treatment and control (ENV, P=0.027). $^{a\text{-}c}$ Columns that do not share a superscript differ significantly (P<0.05).

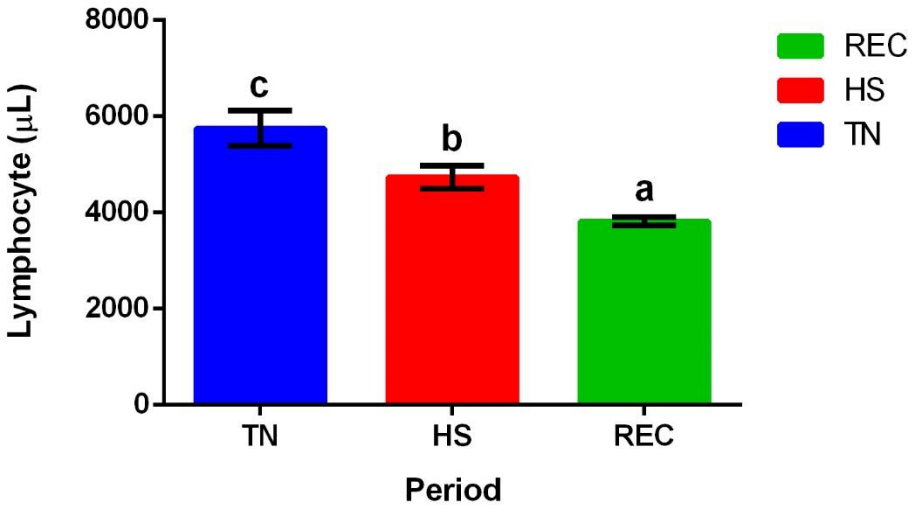

Figure 3.11. Effects of TN (thermoneutral), HS (heat stress), and REC (recovery at TN) on lymphocyte count (µL) with mean of treatment and control (ENV, $P<0.0001$). [a-c] Columns that do not share a superscript differ significantly ($P<0.05$).

Table 3.1. Ingredient composition of diet

Item	% of DM
Alfalfa Hay	47
Lactation Premix	53
Chemical analysis	
CP, %	19.24
NDF, %	27.13
ADF, %	20.21
Fat, %	5.40
DM, %	52.00
NE_L, Mcal/kg	1.72

Table 3.2. Least square means and tests of significance for respiration rates (RR) and rectal temperatures (RT) of cows fed either control diet or yeast blend (YB; PMI Nutritional Additives, Arden Hills, MN) and exposed to thermoneutral (TN), heat stress (HS), or recovery (REC) conditions

	Control			YB				*P*-value[1]				
Measure	TN	HS	REC	TN	HS	REC	Mean SEM	ENV	Day(ENV)	TRT	TRT x ENV	TRT x Day(ENV)
RR (breaths/min)	41.86	85.52	44.78	42.88	84.34	44.27	4.36	<0.0001	0.0058	0.9686	0.8046	0.6437
RT (ºC)	38.27	39.44	38.26	38.13	39.60	38.31	0.20	<0.0001	<0.0001	0.9279	0.3289	0.1826

[1]ENV = environment; TRT = treatment.

Table 3.3. Least square means and tests of significance of dry matter and water intake, milk yield and composition, feed efficiency, and body weight of cows fed control (CON) or yeast blend (YB; PMI Nutritional Additives, Arden Hills, MN) diets exposed to thermoneutral (TN), heat stress (HS), or recovery (REC) conditions

	Control			YB				*P*-value[1]				
Parameter	TN	HS	REC	TN	HS	REC	Mean SEM	ENV	Day(ENV)	TRT	TRT x ENV	TRT x Day(ENV)
DMI (kg)	19.09	17.59	21.95	18.33	15.75	20.33	0.99	<0.0001	<0.0001	0.2880	0.5751	0.4125
Water intake (L)	102.87	114.66	91.86	101.84	123.98	87.32	8.09	<0.0001	0.0077	0.8499	0.420	0.2392
Milk yield (kg)	22.58	21.14	20.91	25.16	22.21	22.36	1.82	0.001	<0.0001	0.5071	0.4498	0.4861
FCM (kg/d)	23.27	22.03	20.01	26.88	23.49	20.78	2.14	0.0011	0.4734	0.4818	0.4060	0.1332
Fat (%)	4.25	4.31	3.57	4.36	4.48	3.66	0.30	0.0129	0.3434	0.6887	0.9872	0.1398
Protein (%)	3.07	2.98	3.04	2.82	2.93	2.98	0.11	0.7983	0.0512	0.3162	0.4575	0.9563
Lactose (%)	4.73	4.65	4.51	4.50	4.82	4.74	0.15	0.6143	0.1319	0.7373	0.2104	0.9143
SCC (x 10,000)	90.31	47.48	39.21	929.06	348.63	380.25	252.05	0.0912	0.3535	0.1278	0.1727	0.2622
Feed Efficiency[2]	1.24	1.29	0.91	1.47	1.51	1.03	0.08	<0.0001	0.0002	0.0519	0.7077	0.3134
BW (kg)	642.48	634.92	628.12	589.12	565.08	556.08	17.58	0.0103	-	0.0235	0.3575	-

[1]ENV = environment; TRT = treatment.
[2]4% FCM/DMI

Table 3.4. Least square means and test of significance for hormones and metabolites of cows fed either control or yeast blend (PMI Nutritional Additives, Arden Hills, MN) diets exposed to thermoneutral (TN), heat stress (HS), or recovery (REC) conditions

	Control			Yeast Blend				*P*-value[1]				
Parameter	TN	HS	REC	TN	HS	REC	Mean SEM	ENV	Day(ENV)	TRT	TRT*ENV	TRT*Day(ENV)
Glucose (mg/dL)	67.96	70.39	69.79	67.75	66.80	65.16	1.64	0.5667	<0.0001	0.1541	0.2377	0.8109
NEFA[2] (µEq/L)	252.75	258.96	248.80	291.94	305.62	240.33	34.37	0.4505	0.0697	0.4016	0.6306	0.0868
BHB[3] (mM)	0.74	0.72	0.57	0.68	0.75	0.59	0.54	0.0009	0.0007	0.9591	0.7412	0.5367
BUN[4] (mg/dL)	4.18	5.03	4.95	4.60	5.71	5.01	0.31	<0.0001	0.0012	0.3471	0.1385	0.1589
Insulin (ng/mL)	0.44	0.49	0.39	0.40	0.56	0.44	0.07	0.0365	0.0103	0.6831	0.576	0.8590
Cortisol (ng/mL)	34.45	52.16	33.81	36.82	51.05	28.94	2.35	<0.0001	<0.0001	0.5047	0.3999	0.9131

[1]ENV = environment; TRT = treatment.
[2]Non-esterified fatty acids
[3]β-hydroxybutyrate
[4]Blood urea nitrogen

Table 3.5. Least square means and test of significance for white blood cell differentials of cows fed either control or yeast blend (PMI Nutritional Additives, Arden Hills, MN) diets exposed to thermoneutral (TN), heat stress (HS), or recovery (REC) conditions.

	Control			Yeast Blend				*P*-value[1]				
Parameter	TN	HS	REC	TN	HS	REC	Mean SEM	ENV	Day(ENV)	TRT	TRT*ENV	TRT*Day(ENV)
Neutrophils (x 10^3 µL)	2.17	2.79	2.76	1.54	3.06	2.51	442.74	0.0272	<0.0001	0.7136	0.4314	0.7709
Lymphocytes (x 10^3 µL)	5.37	4.41	3.80	5.80	5.06	3.83	393.54	<0.0001	<0.0001	0.4556	0.3457	0.4966
Neutrophil/lymphocyte ratio	0.48	0.68	0.80	0.61	0.67	0.67	0.11	0.2186	<0.0001	0.9914	0.5112	0.7976
Total WBC (x 10^3 µL)	8.33	7.98	7.38	9.01	8.94	7.20	0.78	0.0099	0.3959	0.6183	0.4075	0.6334

[1]ENV = environment; TRT = treatment

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